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The Western Journal of Medicine

VOLUME 154 • NUMBER 1 JANUARY 1991

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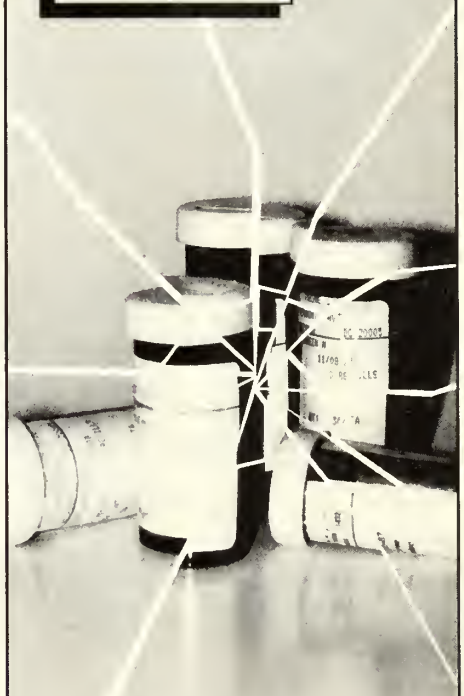

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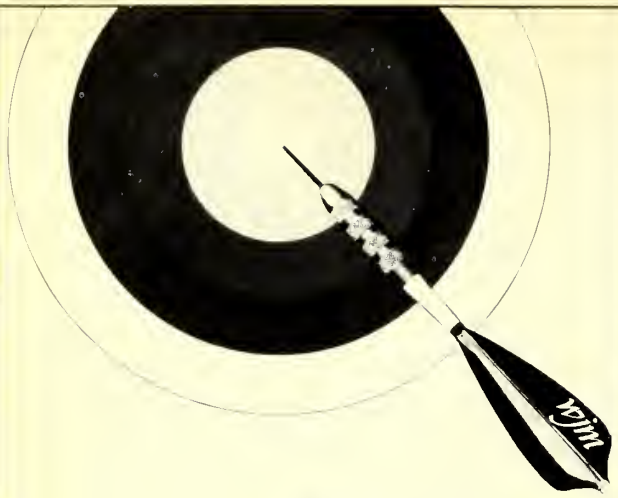
[1] FDA survey, "Patient Receipt of Rx Drug Information", 1983
[2] A Study of Attitudes, Concerns, and Information Needs for Rx Drugs and Related Illnesses, CBS Television Network Consumer Model Survey, 1983



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From the Department of Medicine, Division of Gastroenterology, Center for Ulcer Research and Education, University of California, Los Angeles, School of Medicine, and UCLA Center for the Health Sciences. Presented at the Plenary Session, Western Association of Physicians, Carmel, California, February 6, 1990.

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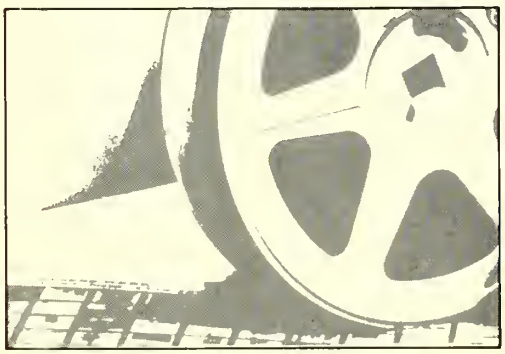

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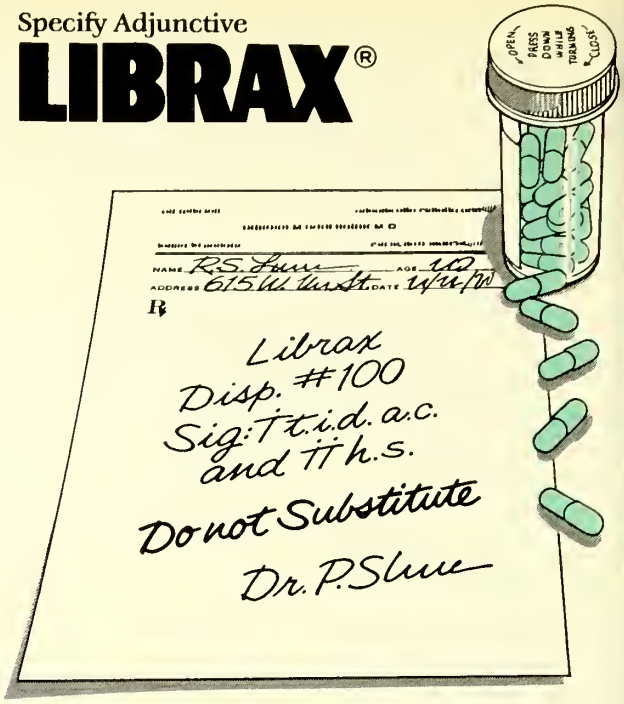

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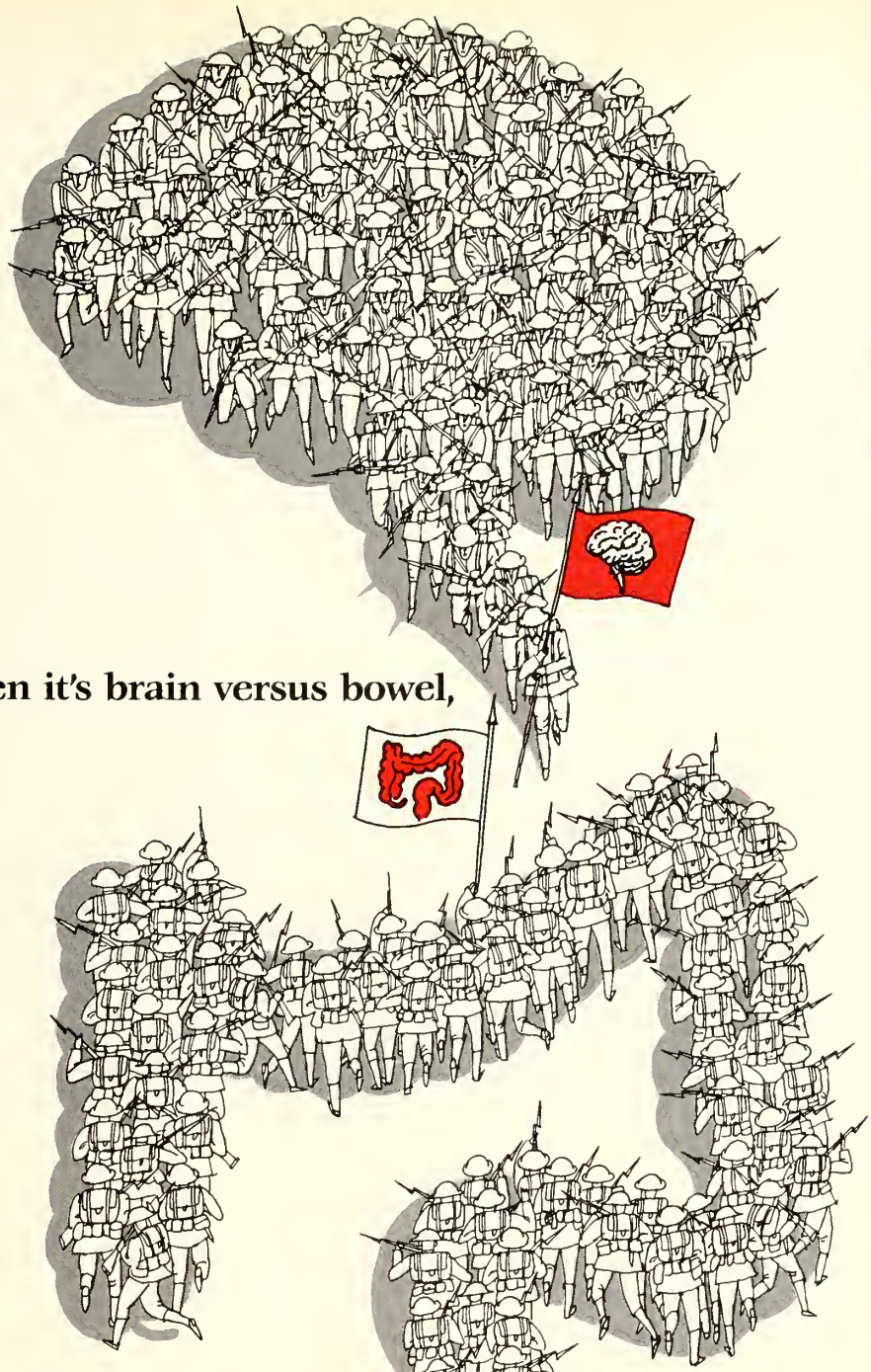

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From the Department of Medicine, Division of Pulmonary and Critical Care Medicine, UCLA Medical Center, Los Angeles, and the Department of Medicine, Divisions of Pulmonary and Critical Care Medicine, and Allergy and Immunology, Santa Barbara Medical Foundation Clinic, Santa Barbara, California.

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Ointment 0.1%
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INDICATIONS AND USAGE ELOCON **Cream, Ointment**, and **Lotion**, are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

CONTRAINDICATIONS ELOCON **Cream, Ointment**, and **Lotion**, are contraindicated in patients who are hypersensitive to mometasone furoate, to other corticosteroids, or to any ingredient in these preparations.

PRECAUTIONS **General:** Systemic absorption of potent topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients

Conditions which augment systemic absorption include application of more potent steroids, application of steroids in optimized vehicles, use over large surface areas, prolonged use, use in areas where the epidermal barrier is disrupted, and the use of occlusive dressings (See **DOSAGE AND ADMINISTRATION**.)

Patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (See **PRECAUTIONS – Pediatric Use**.)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted

In the presence of dermatological infections, use of an appropriate antifungal or antibacterial agent should be instituted If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled

Laboratory Tests The following tests may be helpful in evaluating HPA axis suppression
Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids

Genetic toxicity studies with mometasone furoate, which included the Ames test, mouse lymphoma assay, and a micronucleus test, did not reveal any mutagenic potential

Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels Corticosteroids have been shown to be teratogenic after dermal application in laboratory animals There are no adequate and well-controlled studies of teratogenic effects from topically applied corticosteroids in pregnant women Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother

Pediatric Use: *Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.*

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS The following local adverse reactions were reported with ELOCON **Cream** during clinical studies with 319 patients burning, 1, pruritus, 1; and signs of skin atrophy, 3

The following local adverse reactions were reported with ELOCON **Ointment** during clinical studies with 812 patients burning, 13, pruritus, 8, skin atrophy, 8, tingling/stinging, 7, and furunculosis, 3

The following local adverse reactions were reported with ELOCON **Lotion** during clinical studies with 209 patients acneiform reaction, 2, burning, 4, and itching, 1. In an irritation/sensitization study with 156 normal subjects, folliculitis was reported in 4

The following local adverse reactions have been reported infrequently when other topical dermatologic corticosteroids have been used as recommended These reactions are listed in an approximate decreasing order of occurrence burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria

OVERDOSAGE Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (See **PRECAUTIONS**.)

DOSAGE AND ADMINISTRATION Apply a thin film of ELOCON **Cream** or **Ointment** to the affected skin areas once daily Do not use occlusive dressings.

Apply a few drops of ELOCON **Lotion** to the affected areas once daily and massage lightly until it disappears For the most effective and economical use, hold the nozzle of the bottle very close to the affected areas and gently squeeze

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:
1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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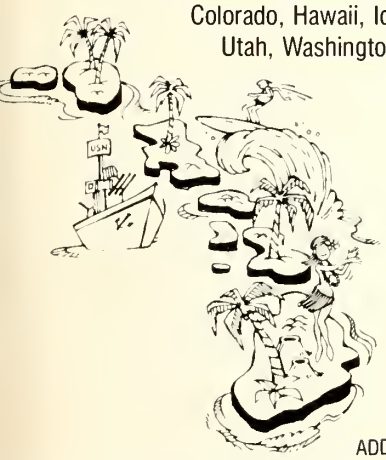

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MICHAEL A. MARLETTA, PhD
Dr Marletta is Associate Professor of Medicinal Chemistry, College of Pharmacy, and Associate Professor of Biological Chemistry, School of Medicine, University of Michigan, Ann Arbor.

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From the Department of Surgery, University of Utah College of Medicine, Salt Lake City. Dr Merrell is currently with the Section of Vascular Surgery, Mayo Clinic, Rochester, Minnesota.

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★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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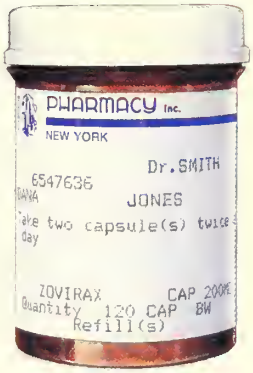

*Alternate maintenance regimens range from 200 mg t.i.d. to 200 mg five times daily.

†In a controlled study of 3 years' duration, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively.[3]

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Genital Herpes Infections: The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs Thus orally administered Zovirax is not appropriate in treating all genital herpes infections The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes)

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy Patients with mild disease may derive less benefit than those with more severe episodes In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered Zovirax given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively Serial analyses of the 3 month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time

The frequency and severity of episodes of untreated genital herpes may change over time After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects In general, orally administered Zovirax should not be used for the suppression of recurrent disease in mildly affected patients Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease Thus, this regimen should be considered only for appropriate patients with annual re-evaluation

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions

Herpes Zoster Infections: In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to Zovirax and 94 to placebo), Zovirax (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to Zovirax and 43 to placebo), Zovirax (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia)

CONTRAINDICATIONS: Zovirax Capsules and Suspension are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations

WARNINGS: Zovirax Capsules and Suspension are intended for oral ingestion only

PRECAUTIONS General: Zovirax has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility) The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION)

Exposure of Herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients The relationship between the *in vitro* sensitivity of Herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY Microbiology)

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve Urinary excretion and renal clearance were correspondingly reduced The clinical effects of this combination have not been studied

Carcinogenesis, Mutagenesis, Impairment of Fertility The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes) Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics)

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay

Acyclovir was tested in two *in vitro* cell transformation assays Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters, higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels) In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels) In all 4 microbial assays, no evidence of mutagenicity was observed Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in man At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels Results in the other five mammalian cell loci follow at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels, at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p o) or in rats (25 mg/kg/day, s c) In the mouse study plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels At a higher dose in the rat (50 mg/kg/day, s c), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels) No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels) In a rat peri- and postnatal study at 50 mg/kg/day s c (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12 5 mg/kg/day and 25 mg/kg/day, s c The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured) However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy Plasma levels were not measured in the one month study and were 24 to 48 times human levels in the six month study Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day, some evidence of recovery of sperm production was evident 30 days postdose Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels No testicular abnormalities were seen in dogs given 50 mg/kg/day i v for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels)

Pregnancy: ***Teratogenic Effects***: Pregnancy Category C Acyclovir was not teratogenic in the mouse (450 mg/kg/day p o) rabbit (50 mg/kg/day, s c and i v) or in standard tests in the rat (50 mg/kg/day, s c) These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity In this test, rats were given 3 s c doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels There are no adequate and well-controlled studies in pregnant women Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of Zovirax and ranged from 0 6 to 4 1 times corresponding plasma levels These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0 3 mg/kg/day Caution should be exercised when Zovirax is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Herpes Simplex: ***Short-Term Administration***: The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with orally administered Zovirax were nausea and/or vomiting in 8 of 298 patient treatments (2 7%) and headache in 2 of 298 (0 6%) Nausea and/or vomiting occurred in 2 of 287 (0 7%) patients who received placebo

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with orally administered Zovirax (0 3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat

Long-Term Administration: The most frequent adverse reactions reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 Zovirax - treated patients were nausea (4 8%), diarrhea (2 4%), headache (1 9%) and rash (1 7%) The 589 control patients receiving intermittent treatment of recurrences with Zovirax for 1 year reported diarrhea (2 7%), nausea (2 4%), headache (2 2%) and rash (1 5%)

The most frequent adverse reactions reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1 5%), rash (1 3%) and paresthesia (0 8%) Reactions reported by 329 patients during the third year include asthenia (1 2%), paresthesia (1 2%) and headache (0 9%)

Herpes Zoster: The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral Zovirax 5 times daily for 7 to 10 days in 323 patients were malaise (11 5%), nausea (8 0%), headache (5 9%), vomiting (2 5%), diarrhea (1 5%) and constipation (0 9%) The 323 placebo recipients reported malaise (11 1%), nausea (11 5%), headache (11 1%), vomiting (2 5%), diarrhea (0 3%) and constipation (2 4%)

OVERDOSAGE: Precipitation of acyclovir in renal tubules may occur when the solubility (2 5 mg/mL) in the intratubular fluid is exceeded Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species rats treated with i v and i p doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s c doses of 100 mg/kg/day for 10 days, rabbits at s c and i v doses of 50 mg/kg/day for 13 days, and dogs at i v doses of 100 mg/kg/day for 31 days A 6 hr hemodialysis results in a 60% decrease in plasma acyclovir concentration Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION)

DOSAGE AND ADMINISTRATION: **Treatment of initial genital herpes**: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 10 days

Chronic suppressive therapy for recurrent disease: 400 mg (two 200 mg capsules or two teaspoonfuls [10 mL] suspension) 2 times daily for up to 12 months, followed by re-evaluation See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily

Intermittent Therapy: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 5 days Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules or four teaspoonfuls [20 mL] suspension) every 4 hours orally 5 times daily for 7 to 10 days

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications

Normal Dosage Regimen (5x daily)	Creatinine Clearance (mL/min/1 73m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval (hrs)
200 mg every 4 hours	> 10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

For patients who require hemodialysis, the dosing schedule should be adjusted so that a dose is administered after each dialysis

References: 1. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection: a multicenter double-blind trial. *JAMA*. 1988;260:201-206. **2.** Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med*. 1988;85(suppl 2A):14-19. **3.** Data on file, Burroughs Wellcome Co., 1990.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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PROCARDIA XL Also Provides Confident 24-Hour Control of Angina[3]

- In patients with angina, doses above 90 mg should be used with caution and only when clinically warranted

References:

1. Chung M, Reitberg DP, Gaffney M, Singleton W. Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system: a controlled-release formulation of nifedipine. *Am J Med.* 1987;83(suppl 6B):10-14. **2.** Bravo EL, Krakoff LR, Tuck MK, Friedman CP, the MATH Study Group. Effects of nifedipine gastrointestinal therapeutic system (NGITS) in older (O) and younger (Y) essential hypertensives. *Clin Pharmacol Ther.* 1990;47:199. Abstract. **3.** Bittar N. Usefulness of nifedipine for myocardial ischemia and the nifedipine gastrointestinal therapeutic system. *Am J Cordiol.* 1989;64:31F-34F.

Brief Summary

PROCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use

CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine

WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery

The following information should be taken into account in those patients who are being treated for hypertension as well as angina

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction

Other: As with any other non-deformable material, caution should be used when administering PROCARDIA XL in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of PROCARDIA XL.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS.) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PROCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic*: asthenia, flushing, pain; *cardiovascular*: palpitations; *central nervous system*: insomnia, nervousness, paresthesia, somnolence; *dermatologic*: pruritus, rash; *gastrointestinal*: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal*: arthralgia, leg cramps; *respiratory*: chest pain (nonspecific), dyspnea; *urogenital*: impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic*: face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular*: arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system*: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo; *dermatologic*: alopecia, increased sweating, urticaria, purpura; *gastrointestinal*: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal*: back pain, gout, myalgias; *respiratory*: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses*: abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive*: breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8%, compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood changes (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 8% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine.

More detailed professional information available on request. Revised July 1990

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Azmacort®
(triamcinolone acetonide)
inhaler

For Oral Inhalation Only

Brief Summary

DESCRIPTION: Azmacort (triamcinolone acetonide) is an anti-inflammatory steroid

INDICATIONS: Azmacort (triamcinolone acetonide) inhaler is indicated only for patients who require chronic treatment with corticosteroids for the control of the symptoms of bronchial asthma. Such patients would include those already receiving systemic corticosteroids and selected patients who are inadequately controlled on a non-steroid regimen and in whom steroid therapy has been withheld because of concern over potential adverse effects.

Azmacort inhaler is *NOT* indicated

1. For relief of asthma which can be controlled by bronchodilators and other non-steroid medications.
2. In patients who require systemic corticosteroid treatment infrequently
3. In the treatment of non-asthmatic bronchitis.

CONTRAINDICATIONS: Azmacort inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: Particular care is needed in patients who are transferred from systemically active corticosteroids to Azmacort inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosolized steroids in recommended doses. After withdrawal from systemic corticosteroids, a number of months is usually required for recovery of hypothalamic-pituitary-adrenal (HPA) function. For some patients who have received large doses of oral steroids for long periods of time before therapy with Azmacort inhaler is initiated, recovery may be delayed for one year or longer. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis or other conditions with acute electrolyte loss. Although Azmacort inhaler may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies only normal physiological amounts of corticosteroid systemically and does NOT provide the increased systemic steroid which is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been recently withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Localized infections with *Candida albicans* have occurred infrequently in the mouth and pharynx. These areas should be examined by the treating physician at each patient visit. The percentage of positive mouth and throat cultures for *Candida albicans* did not change during a year of continuous therapy. The incidence of clinically apparent infection is low (2.5%). These infections may disappear spontaneously or may require treatment with appropriate antifungal therapy or discontinuance of treatment with Azmacort inhaler.

Azmacort inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma which are not responsive to bronchodilators occur during the course of treatment with Azmacort inhaler. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by the administration of Azmacort inhaler in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone.

Theoretically, the use of inhaled corticosteroids with alternate day prednisone oral therapy should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to Azmacort inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS: During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function (See DOSAGE AND ADMINISTRATION for details). Although steroid withdrawal effects are usually transient and not severe, severe and even fatal exacerbation of asthma can occur if the previous daily oral corticosteroid requirement had significantly exceeded 10 mg/day of prednisone or equivalent.

In responsive patients, inhaled corticosteroids will often permit control of asthmatic symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since triamcinolone acetonide is absorbed into the circulation and can be systemically active, the beneficial effects of Azmacort inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

Suppression of HPA function has been reported in volunteers who received 4000 mcg daily of triamcinolone acetonide. In addition, suppression of HPA function has been reported in some patients who have received recommended doses for as little as 6-12 weeks. Since the response of HPA function to inhaled corticosteroids is highly individualized, the physician should consider this information when treating patients.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects including suppression of growth in children. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of a decrease in adrenal function.

The long-term effects of triamcinolone acetonide inhaler in human subjects are not completely known, although patients have received Azmacort inhaler on a continuous basis for periods of two years or longer. While there has been no clinical evidence of adverse experiences, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea and lung are also unknown.

The potential effects of Azmacort inhaler on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. For this reason, since systemic administration of corticosteroids may mask some signs of fungal, bacterial or viral infection, the same caution should be observed when treating patients with Azmacort inhaler. The potential effects of long-term administration of Azmacort inhaler on lung or other tissues are unknown. However, pulmonary infiltrates with eosinophilia have occurred in patients receiving other inhaled corticosteroids.

Pregnancy: Pregnancy Category D. Azmacort (triamcinolone acetonide) has been shown to be teratogenic in rats and rabbits when given in doses comparable to the highest dose recommended for human use (approximately 0.032 mg/kg/day). Administration of aerosol inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes.

Teratogenic effects in both species included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. These findings represent known effects of glucocorticoids in laboratory animals.

There are no well-controlled studies in pregnant women. Experience with other dosage forms of triamcinolone acetonide does not include any positive evidence of adverse effects on the fetus. However, since such experience cannot exclude possibility of fetal damage, Azmacort inhaler should be used during pregnancy only if the benefit clearly justifies the potential risk to the fetus. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for triamcinolone acetonide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: A few cases of oral candidiasis have been reported (see WARNINGS). In addition, some patients receiving Azmacort inhaler have experienced hoarseness, dry throat, irritated throat and dry mouth. Increased wheezing and cough have been reported infrequently as has facial edema. These adverse effects have generally been mild and transient.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

See Product circular for full prescribing information.

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1. Bone RC. Control of the late-phase pulmonary response is paramount. A step care strategy for asthma management. *J Respir Dis* 1988;9(11):104-117. 2. Fulliers CJ, Petraco AJ. Control of asthma with triamcinolone acetonide aerosol inhalations at 12-hour intervals. *J Asthma* 1982;19(4):241-247. 3. Grieco MH, Larsen K, Petraco AJ. In vivo comparison of triamcinolone and beclomethasone inhalation delivery systems. *Ann Allergy* 1980;45(4):231-234. 4. Golub JR. Long term triamcinolone acetonide aerosol treatment in adult patients with chronic bronchial asthma. *Ann Allergy* 1980;44(5):131-137.

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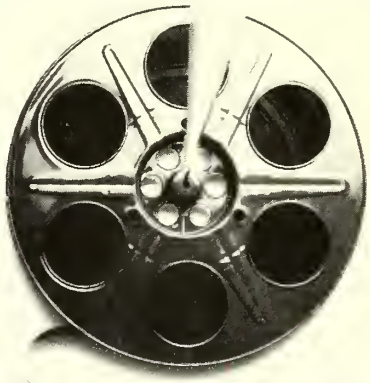

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 19—**Current Topics in Anesthesia.** Mayo Clinic-Scottsdale. Sat. Contact: Trish Gean, (602) 391-8300.

January 26—**Current Issues in Nephrology and Hypertension.** Ashton B. Taylor Auditorium, Mayo Clinic-Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724 (602) 626-6707.

February 10-14—**International Congress IV: Endovascular Therapies in Vascular Disease.** Arizona Heart Institute and American College of Angiology at The Phoenician Resort, Scottsdale. Sun-Thur. Contact: Erika Scott, (602) 266-2200.

February 15-17—**Anesthesia for the '90s: 17th Annual Scientific Meeting.** Arizona Society of Anesthesiologists at Wyndham Paradise Valley Resort, Paradise Valley. Fri-Sun. Contact: Beverly Reichter, (602) 246-8901.

February 21-23—**17th Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell, (602) 820-7027.

February 28-March 2—**13th Annual Postgraduate Course: Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix OB/GYN Society at the Scottsdale Hilton Hotel, Scottsdale. Thurs-Sat. Contact: (602) 266-6321.

February 28-March 3—**Arizona Academy of Family Physicians Annual Scientific Assembly.** Scottsdale Plaza Resort. Thurs-Sun. Contact: Nancy Reeves, (602) 249-2021.

March 2—**ENT for the Primary Care Physician.** Ashton B. Taylor Auditorium, Mayo Clinic-Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

March 16-20—**Fifth Annual Magnetic Resonance Imaging Conference.** Barrow Neurological Institute at Marriott's Camelback Inn, Scottsdale. Sat-Wed. Contact: Kevin King, RT, (602) 285-3956.

April 25—**Clinical Reviews 1991.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Thurs. Contact: Mayo Clinic-Scottsdale.

April 27—**Gastroenterology: Update for the Family Practitioner.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Sat. Contact: Mayo-Clinic Scottsdale.

April 27—**Urology for the Primary Care Physician.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 20-26—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Hotel, Poipu Beach, Kauai. Sun-Sat. 20 hrs. $345. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 25-27—**29th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Pediatric Anesthesiology Foundation at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054.

February 3-8—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray Atnikov, MD, c/o PO Box F110-63, Blaine, WA 98230. (604) 874-5291.

March 23-24—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Newport Beach Marriott. Sat-Sun. 9 hrs. $150. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428 (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024 (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

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May 16-19—**California Society of Anesthesiologist's Annual Meeting.** CSA at Marriott Hotel, Anaheim. Thurs-Sun. 20 hrs. $175. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

CARDIOLOGY

January 24-26—**Cardiology '91.** Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564.

February 13—**31st Annual Cardiology Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Building, Chico. Wed. Contact: Linda Spring, (916) 891-7375.

April 2-4—**1st Annual Symposium of Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. $750. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 22-May 1—**Cardiology for the Consultant: A Physician's Retreat.** Scripps Clinic and Research Foundation at Inn Rancho Santa Fe. 1½ wks. Contact: Mary Ann Morris, 860 SW Scherer Rd, Lee's Summit, MO 64063. (816) 524-5780.

DERMATOLOGY

January 17-19—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $400. Contact: Susan J Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 24-26—**Cutaneous Malignancies: 1991 Skin Cancer Update.** Scripps Clinic and Research Foundation at Hyatt Regency, La Jolla. Thurs-Sat. 12 hrs. $350. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

January 14-18—**Emergency Medicine Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at Hyatt Regency, La Jolla. 32 hrs. $485. Contact: UCSD.

February 24-March 1—**Annual Emergency Medicine.** UCD at Hyatt Lake Tahoe, Incline Village, NV. Sun-Fri. 25 hrs. $465. Contact: UCD.

March 10-15—**12th Annual Mammoth Mountain Emergency Medicine Ski Conference.** CAL/ACEP at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Medical Conferences, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 18-22—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

April 3-6—**Advances in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Sat. 22 hrs. $435. Contact: UCSF.

May 6-10—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. 32 hrs. $485. Contact: UCSD.

June 8-9—**Clinical Toxicology and Emergency Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $310. Contact: UCSF.

June 24-28—**Postgraduate Institute for Primary Care & Emergency Physicians Emergency Medicine Symposium III: Pediatrics, OB/GYN, Dermatology, Legal Aspects, Etc.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $260-$485. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

January 18-20—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at San Diego Princess Resort. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

January 26-February 2—**Vascular Update 1991.** University of Washington School of Medicine at Westin Hotel, Kauai, Hawaii. One week. Contact: U/W School of Medicine, Div of CME, SC-50, Seattle 98195. (206) 543-1050.

January 31-February 2—**Adolescent Medicine for the Practitioner.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-9592.

February 1-2—**Pediatric Dermatology for the Primary Care Physician.** UCSF at Le Meridien Hotel, San Francisco. Fri-Sat. 10 hrs. $250. Contact: UCSF.

February 1-8—**Nevada Academy of Family Physicians Annual CME/Ski Meeting with Optional Colposcopy Certification.** NAFP at Caesars Hotel, Stateline (Lake Tahoe), Nevada. Sun-Fri. 48 hrs. Contact: Dottie Batchelor, PO Box 7471, Reno, NV 89510. (702) 826-5100.

February 11-15—**Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

February 15-17—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 15-18—**43rd Scientific Assembly of the California Academy of Family Physicians.** CAFP at Wyndham Hotel, Palm Springs. Fri-Mon. 23 hrs. Contact: Robert Fagan, (415) 541-0762.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Research Foundation and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

March 15-17—**Psychopharmacology for the Primary Care Physician.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 16—**Orthopedics and Sports Medicine in Primary Care.** Scripps Clinic and Research Foundation at Amphitheater of the Green Hospital, La Jolla. Sat. 6 hrs. $125. Contact: Laurie Jones, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

March 27-29—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Cathedral Hill Hotel, San Francisco. Wed-Fri. 16 hrs. Contact: UCSF.

April 6-13—**Primary Care Medicine: Update '91.** UCSF at Waiohai Kauai, Hawaii. 1 week. 20 hrs. $525. Contact: UCSF.

April 26-28—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village, San Diego. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 10-14—**UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

INTERNAL MEDICINE

January 16—**20th Annual Respiratory Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Building, Chico. Wed. Contact: Linda Spring, (916) 891-7375.

January 31-February 2—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thurs-Sat. 17 hrs. $350. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 1-3—**8th Annual Reider Laser Symposium-Urology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact: UCI.

February 3-8—**Winter Urologic Forum.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 22 hrs. $400. Contact: UCD.

February 15-17—**24th Annual Recent Advances in Neurology.** UCSF at San Francisco. Fri-Sun. 15 hrs. Contact: UCSF.

February 18-20—**Clinical Hematology and Oncology: 1991.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 1—**17th Annual Diabetes Symposium.** UCD at Sheraton Hotel, Sacramento. Fri. 6 hrs. $140. Contact: UCD.

March 6-7—**Advances in Endocrinology and Metabolism.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 8-9—**Diabetes Update.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

March 11-15—**29th Annual Symposium on Critical Care Medicine.** Mon-Fri. 25 hrs. $435-$670. Contact: USC.

March 15-21—**Internal Medicine 1991: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 20—**Growth Factors in Clinical Medicine.** Scripps Clinic and Research Foundation at La Jolla. Sat. 4 hrs. $75. Contact: Laurie Jones, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

May 13-17—**Advances in Internal Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $585. Contact: UCSF.

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American Academy of Pediatrics

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OB/GYN

February 1-3—**8th Annual Reider Laser Symposium-Gynecology.** Memorial/UCI Center for Health Education at Palm Springs. Fri-Sun. Contact. UCI.

February 3-5—**Ambulatory Gynecology Update.** UCD at Hyatt Regency Incline Village, Nevada. Sun-Tues. 12 hrs. $230. Contact: UCD.

February 3-8—**OB/GYN Update: 1991.** UCD at Hyatt Lake Tahoe Incline Village, NV. Sun-Fri. Contact: UCD.

February 14-17—**46th Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB-GYN Assembly, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514

March 9—**Infertility Update VI.** Scripps Clinic and Research Foundation. Sat. 7 hrs. $145. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 13-17—**Gynecologic Surgery with Special Emphasis on Pre-Invasive Neoplasia and Urogynecology.** UCI/Memorial Center for Health Education at La Quinta Hotel Golf & Tennis Resort, Palm Springs. Wed-Sun. Contact. UCI.

April 10-14—**Pacific Coast Fertility Society Annual Scientific Program.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No 500, Los Angeles 90036. (213) 937-5514.

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

January 17-18—**Pesticides and Medicine in Hawaii.** Hawaii Medical Association at Ala Moana Hotel, Honolulu, Hawaii. Thurs-Fri. 15 hrs. $190. Contact: Hawaii Medical Association, 1360 S Beretania St, Honolulu, HI 96814. (808) 536-7702.

January 28-February 8—**Occupational and Environmental Medicine: Session I.** UCSF at Cathedral Hill Hotel, San Francisco. 1½ weeks. 80 hrs. $1,200. Contact: UCSF.

February 11-15—**Occupational and Environmental Medicine: Session III.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

March 13-17—**Mountain Medicine: '91.** American College of Emergency Physicians at Squaw Valley. Wed-Sun. 22 hrs. $395. Contact: Howard Donner, MD, PO Box 321, Yreka 96097. (800) 888-5632.

OPHTHALMOLOGY

February 3-7—**10th Annual Squaw Valley Retina Symposium.** Alta-California Ophthalmological Society at Squaw Valley Inn, Olympic Valley. Sun-Thurs. 16 hrs. Contact: Mercy General Hospital, Community Relations, 4001 "J" St, Sacramento 95819. (916) 454-4410.

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center, Los Angeles. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

March 23—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. $120. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

May 17-19—**California Association of Ophthalmology Annual Meeting.** CAO at Sheraton Grande Torrey Pines, La Jolla. Fri-Sun. Contact: Linda Xyz, (415) 777-3937.

OTOLARYNGOLOGY

February 8-10—**60th Midwinter Clinical Conference.** Research Study Club of Los Angeles at Moseley/Salvatori Conference Center. Fri-Sun. Contact: Research Study Club, PO Box 1216, Murrieta 92362. (714) 677-4482.

January 18-20—**Triological Society Western Section.** Triological Society at Santa Barbara Biltmore Hotel. Fri-Sun. Contact: David Hilding, MD, Ste 1, Hospital Dr, Price, UT 84501. (801) 637-4327.

PATHOLOGY

February 1-2—**9th Annual Infectious Disease Update.** UCD at Hilton Inn, Sacramento. Fri-Sat. 11 hrs. $175. Contact: UCD

February 13-15—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at Hyatt Regency Hotel, La Jolla. Wed-Fri. 21 hrs. $375. Contact: Laurie Jones, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

April 6—**6th Annual Conference: New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Amphitheater of Green Hospital, La Jolla. Sat. 7 hrs. $125. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

April 17-19—**12th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. $395. Contact: UCSF.

PEDIATRICS

January 23-26—**Health Science Response to Child Maltreatment 1991.** Children's Hospital San Diego at U S Grant Hotel, San Diego. Wed-Sat. 22 hrs. Contact: Children's Hospital, (619) 576-5814.

February 8-10—**Current Concepts in Pediatric Medicine 1991.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Contact: CME Dept. Children's Hospital, (619) 576-4072.

February 13-15—**16th Annual Symposium on Care of the Sick Newborn.** Memorial UCI Center for Health Education at Hyatt Regency Hotel, Long Beach. Wed-Fri. Contact: UCI.

February 18-20—**Pediatrics Update: 1991.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5-6—**Annual Ambulatory Pediatrics.** UCD at Radisson Hotel, Sacramento. Fri-Sat. Contact: UCD.

April 11-13—**Nevada Neonatal-Pediatric Conference.** Humana Children's Hospital at Sands Hotel and Casino, Las Vegas. Thurs-Sat. 15 hrs. $200. Contact: Evelyn Bethel, (702) 733-4944.

April 13-14—**Pediatric Update 1991.** Children's Hospital Oakland at Jack London's Waterfront, Oakland. Sat-Sun. 11 hrs. $250. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

April 18-19—**10th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. Contact: UCD.

May 16-18—**24th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 21-23—**Current Concepts in Child Neurology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 15 hrs. Contact: Children's Hospital, (619) 576-4072.

PSYCHIATRY

January 27-February 1—**17th Annual Midwinter Program for Psychiatrists: Special Focus on Psychic Trauma.** UCD at Hyatt Regency, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 23-24—**The Male Mystique: New Perspectives on the Psychology of Men.** San Diego Psychoanalytic Society and Institute at Hotel del Coronado, San Diego. Sat-Sun. Contact: Joyce Harding, SDPSI, 1010 Turquoise St, Ste 320, San Diego 92109-1259. (619) 488-0687.

February 28-March 1—**The Dimensions of Caring 1991: A Symposium on Palliative Care of the Cancer Patient.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Fri. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

March 2-3—**Basic Hypnosis: A Hands-On Workshop.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 16 hrs. $195-$295. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (213) 475-1260.

April 27-28—**The Cutting Edge: Being a Better Therapist.** UCSD at La Jolla Marriott, San Diego. Sat-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

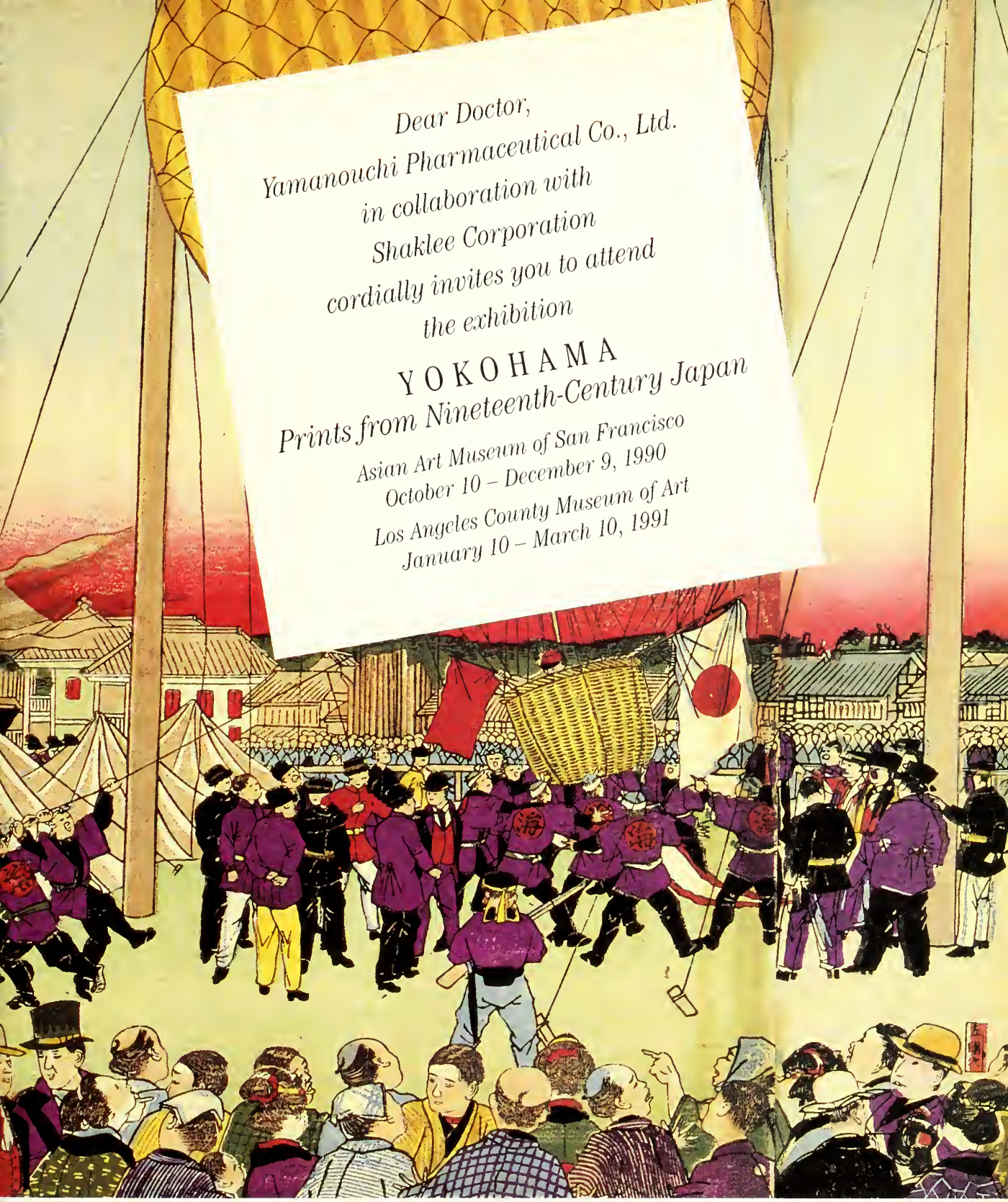
RADIOLOGY

January 19-21—**Advanced Seminars in Diagnostic Imaging.** UCSF at Ritz-Carlton Resort Hotel, Laguna Niguel. Sat-Mon. 20 hrs. $400. Contact: UCSF.

February 1-3—**43rd Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 17 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 4-5—**Angio-Interventional Radiology.** UCSD at Le Meridien Hotel, San Diego. Mon-Tues. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 30)



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CONTINUING MEDICAL EDUCATION

(Continued from Page 28)

Feburary 4-8—**Magnetic Resonance Imaging in the Desert.** UCSF at Ritz-Carlton, Rancho Mirage. Mon-Fri. 22 hrs. $595. Contact: UCSF.

February 5-9—**17th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Maui Marriott Hotel, Maui, Hawaii. Tues-Sat. 16 hrs. $395. Contact: LARS, PO Box 91215, Los Angeles 90009. (213) 827-9078.

February 6—**Intraluminal Ultrasound.** UCSD at Le Meridien Hotel, San Diego. Wed. 6 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 6-9—**Introduction to Doppler Principles.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 7 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 6-9—**Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Wed-Sat. 22 hrs. $495. Contact: UCSD

February 9-10—**Obstetric and Gynecology Sonographic Update: Focus on CNS Abnormalities.** UCSD at Le Meridien Hotel, San Diego. Sat-Sun. 10 hrs. $150. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 11-15—**Contemporary Diagnostic Imaging Featuring MRI, CT, US and Interventional Radiology.** Stanford University at Ritz-Carlton Hotel, Mauna Lani, Hawaii. Mon-Fri. 20 hrs. $515. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 1-3—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 4-8—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 16-18—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. 16 hrs. $350. Contact: UCSF.

April 7-12—**Diagnostic Imaging: 1991.** UCSF at Ritz-Carlton Mauna Lani, Kona, Hawaii. Sun-Fri. 23 hrs. $595. Contact: UCSF.

April 21-26—**11th Annual San Diego Resident's Radiology Review Course.** UCSD at Hyatt Regency Hotel, La Jolla. Sun-Fri. 39 hrs. $435. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 27—**Introduction to Interventional Radiology.** UCSD at Hyatt Regency Hotel, La Jolla. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

January 9-12—**Biological Basis of Substance Abuse.** UCLA at Loews Santa Monica Beach Hotel. Wed-Sat. 23 hrs. $375. Contact: UCLA.

January 23-26—**6th International Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy.** UCSD at Sheraton Harbor Island East Hotel, San Diego. Wed-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 7-9—**Biotherapy of Cancer: A Symposium for Clinicians and Nurses.** Hoag Hospital at Newport Beach Marriott. Thurs-Sat. 15 hrs. $375. Contact: Nomi Feldman, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

February 18-20—**11th Betty Ford Center Conference on Chemical Dependency.** Annenberg Center for Health Science. Mon-Wed. Contact: ACHSE, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

March 6-8—**11th Annual Current Approaches to Radiation, Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $325. Contact: UCSF.

May 17-18—**What's New in Rehabilitation?** Memorial/UCI Center for Health Education at Queen Mary, Long Beach. Fri-Sat. Contact: UCI.

SURGERY

January 1991-June 1991—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. 5 days per month. 53 hrs. $975. Contact: Antonio de la Cruz, MD, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext. 7079.

January 18-19—**What's New in General Surgery: 13th Annual Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Fri-Sat. 14 hrs. $260. Contact: UCD.

May 2-4—**Advances in Knee Reconstruction Surgery: Ligament Reconstruction, Unicompartmental Replacement, and Patellofemoral Joint.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 26 hrs. $600. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 15-19—**13th Annual Wound Management Workshop: May.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: UCSD.

MULTIPLE TOPICS

March 7-9—**Recent Advances in Geriatric Medicine: New Treatment Options for Old Problems.** UCSD at Pan Pacific Hotel, San Diego. Thurs-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 22-23—**Gender Differences in Nutrition: Annual Clinical Nutrition Program.** UCD at Embassy Suites, Napa. Fri-Sat. Thurs-Fri. Contact: UCD.

April 25-28—**Nevada State Medical Association Annual Meeting.** NSMA at Quail Lodge, Carmel. Thurs-Sun. Contact: Nevada State Medical Association, 3660 Baker Ln, Reno, NV 89502. (702) 825-6788.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 17—**Colorado Radiological Society.** Hyatt Regency DTC, Denver. Thurs. Contact: Carol Goddard, (303) 770-6048.

January 26-31—**Uveitis and Pathology.** Colorado Ophthalmological Society at Westin Hotel, Vail. Sat-Thurs. Contact: Carol Goddard, (303) 770-6048.

February 6-10—**Update on Clinical Allergy: Immunology.** National Jewish Center for Immunology and Respiratory Medicine at Keystone Resort, Keystone. Wed-Sun. Contact: Jeri Wagner, (303) 398-1828.

February 9-16—**16th Annual Psychiatry Conference.** Rose Medical Center at Lion Square Lodge, Vail. One week. Contact: David R. Scott, Rose Medical Center Conference Program, 1 (800) 525-5810.

February 9-16—**13th Annual Emergency Medicine Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 16-23—**17th Annual Obstetrics and Gynecology Conference.** Rose Medical Center, Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 16-23—**16th Annual Internal Medicine Conference.** Rose Medical Center at Lion Square Lodge, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 23-March 2—**16th Annual General Surgery Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 23-March 2—**Fourth Annual Medical Care in the '90s Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 2-9—**13th Annual Pediatrics Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 2-9—**Second Annual Infectious Disease Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 9-16—**16th Annual Primary Care Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

(Continued on Page 114)

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ACP

How to Register

ACP Membership: Consult your Advance Program mailed in December, containing information about the meeting and how to register.

Non-members: Watch for the complete schedule of events and a registration form in the Annual Session Digest appearing in the December 15, 1990, and January 1 and February 1, 1991, issues of ANNALS OF INTERNAL MEDICINE.

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PD-56-JA-6550-A1(10-90)

Biomedical Science

Gastrin—A Normal and Pathologic Regulator of Gastric Function

JOHN H. WALSH, MD, *Los Angeles, California*

Presented at the Plenary Session, Western Association of Physicians, Carmel, California, February 6, 1990.

The stomach presents an unusual interface between the external environment and the endocrine system. The stomach is an endocrine organ, one of the largest in the body, in which many of the regulatory events occur in its lumen. The main stimulants of the gastrin cells are dietary substances such as protein. The product of the parietal cell, acid, acts within the lumen to inhibit antral gastrin cells. Acid is a feedback inhibitor of antral gastrin cells. When acid secretion is prevented, there is disturbance of the feedback inhibition of gastrin release. The development of strong acid-inhibiting drugs has allowed us to study secondary effects of hypergastrinemia independent of the acid-stimulating effects. In my brief review I will discuss hypergastrinemia, the role of gastrin as a regulator of acid secretion, the regulation of gastrin itself, and the trophic effects of gastrin on growth of the gastric mucosa and the potential of gastrin to produce enterochromaffin-like cell tumors of the stomach.

Causes of Hypergastrinemia

There are two major circumstances under which circulating gastrin is increased. One is end-organ failure—that is, the failure to secrete acid. A loss of acid secretion is classically produced by pernicious anemia, by other kinds of antral-sparing atrophic gastritis, or by vagotomy. Recently the development of omeprazole and other long-acting acid inhibitors has permitted the study of the reversible inhibition of acid secretion leading to hypergastrinemia.

The second cause is pathologic hypergastrinemia in which acid secretion is increased owing to the ectopic or poorly regulated production of gastrin. The most common cause of pathologic hypergastrinemia is gastrinoma. This type of disorder can be controlled by H_2 blockers or by hexokinase-adenosine triphosphatase (ATPase) inhibitors. It is now easy to control conditions of acid hypersecretion including the Zollinger-Ellison syndrome and severe acid peptic disorders, such as peptic ulcer and reflux esophagitis. A single dose of omeprazole can lower the markedly increased acid secretion in a gastrinoma patient over a 24-hour period. A question that emerges is whether there are secondary effects of acid suppression that are worrisome.

Role of Gastrin in Normal Gastric Physiology

What is the role of gastrin as a physiologic regulator of gastric secretion? Gastrin is a mixture of larger (G-34) and smaller (G-17) peptides produced from a well-characterized precursor. It is released by the G cells into the blood and acts on receptors that are probably located on both parietal cells and histamine cells. It is one of the stimulants of parietal cell acid secretion, along with histamine and acetylcholine. Interaction of any of these stimulants with its specific receptor leads to activation of the hydrogen potassium ATPase, which can be blocked by inhibitors such as omeprazole.

It is well known that H_2 blockers inhibit acid secretion, indicating a physiologic role for endogenous histamine. Anticholinergic drugs inhibit acid secretion, indicating that acetylcholine receptors also are physiologically important for parietal cell activation. There has been a question as to whether gastrin is an important acid-regulating hormone, primarily because of the absence of specific antagonists.

We recently have developed a monoclonal antibody that is suitable for the in vivo blocking of gastrin. We used this antibody to block the effects of exogenous gastrin and also to study acid secretion stimulated by liquid meals and simultaneously have measured acid secretion by the method of intragastric titration originally devised by Fordtran.[1] Liquid meals are introduced into the stomach, and the production of acid is quantitated by titration at a constant pH. Using this system, we have been able to show that exogenous gastrin and endogenously released gastrin produce similar acid stimulatory responses, suggesting that gastrin is an important hormone (Figure 1). When graded increasing concentrations of peptone were introduced into the stomach, a dose-response curve of increasing plasma gastrin and increasing acid secretion was obtained. This curve was similar to the curve of the responses obtained by infusing gastrin exogenously. These results suggest, but do not prove, a physiologic role for gastrin.

As suitable receptor antagonists of gastrin were not available, we developed a monoclonal antibody that, when injected intravenously, selectively inhibits the acid response to gastrin. In dogs, we have shown that this monoclonal antibody greatly inhibits the acid response to liquid meals, indicating a physiologic role for gastrin in stimulating acid secretion (Figure 2). This antibody is specific and has no effect on the acid response to histamine.

Regulation of Gastrin Release

Having established that gastrin is an important hormone, it is also of interest to know how its secretion is regulated. The gastrin cell is located in the mucosa of the stomach. In

(Walsh JH: Gastrin—A normal and pathologic regulator of gastric function. West J Med 1991 Jan; 154:33-35)

From the Department of Medicine, Division of Gastroenterology, Center for Ulcer Research and Education, University of California, Los Angeles, UCLA School of Medicine, and UCLA Center for the Health Sciences.

Reprint requests to John H. Walsh, MD, Chief, Division of Gastroenterology, UCLA School of Medicine, 44-146 Center for the Health Sciences, 10833 Le Conte Ave, Los Angeles, CA 90024-1684.

ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
ECL = enterochromaffin-like

the same vicinity are D cells that produce somatostatin. Somatostatin is a potent inhibitor of gastrin synthesis and release. Our current model of antral endocrine function includes a paracrine role for somatostatin as an inhibitor of gastrin release. It is difficult to study paracrine function, however, because the regulatory substance is not released into the blood where it can be measured easily, but is released locally. Concentrations of peptides in tissue are difficult to sample and measure.

We have used two methods to study the role of somatostatin in gastrin release. First, we have studied somatostatin and gastrin synthesis by measuring somatostatin and gastrin messenger RNA in antral tissue. Second, we have used monoclonal antibody against somatostatin to interfere with its endogenous function.

In general, there is a reciprocal relationship between somatostatin synthesis and gastrin synthesis and release. When achlorhydria is produced, gastrin increases in tissue and blood are accompanied by a pronounced decrease in antral somatostatin synthesis. Different methods of producing achlorhydria lead to similar changes in somatostatin mRNA and gastrin mRNA. Pharmacologic acid inhibition by omeprazole leads to a notable fall in somatostatin mRNA and the stimulation of gastrin mRNA. Resection of the acid-secreting stomach causes an even greater increase in gastrin mRNA with a similar change in somatostatin mRNA.

During fasting, gastrin mRNA decreases over a period of 24 to 48 hours (Figure 3). Tissue peptide content decreases somewhat more slowly. Somatostatin mRNA is increased within 12 hours and remains at this level during fasting. On refeeding, there is not only a rapid increase in gastrin mRNA and a somewhat slower decrease in somatostatin mRNA, but there is also a rapid increase in tissue gastrin (Figure 4). During fasting, gastrin accumulates not only in its active form, but also as incompletely processed forms. Processing to active forms also is stimulated by feeding. The body thus is well prepared to rest the stomach metabolically when food is not present and to rapidly reactivate gastric metabolism when food is ingested.

One model for the study of paracrine regulation of somatostatin release in the antrum is urethane anesthesia in rats. We recently found that when rats are anesthetized with urethane, acid secretion and gastrin both decrease markedly.

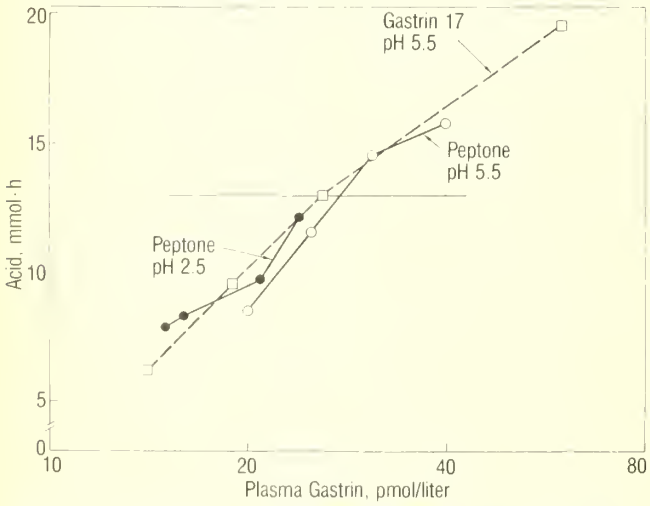

Figure 1.—The graph shows acid secretion in humans as a function of circulating gastrin concentrations. Acid secretion was measured by intragastric titration. The open squares indicate responses to graded doses of intravenously infused gastrin 17. The open circles indicate responses to graded concentrations (1%, 2%, 4%, and 8%) of peptone maintained at an intragastric pH of 5.5; the closed circles indicate responses to the same concentrations of peptone maintained at pH 2.5.

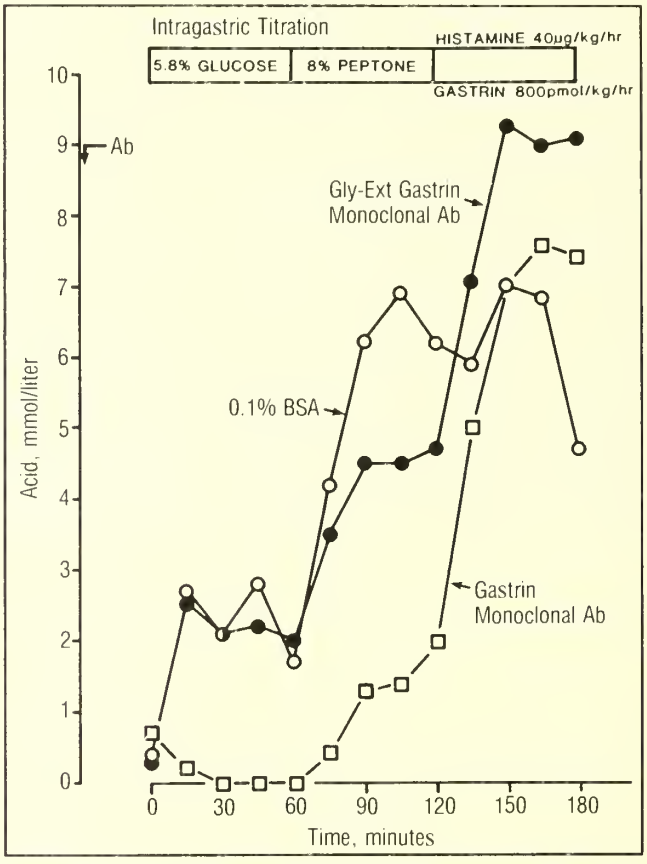

Figure 2.—Acid secretory responses in 8 dogs are shown during control conditions and after the administration of an immunoneutralizing dose of gastrin monoclonal antibody (Ab; open squares). Secretion was stimulated sequentially by distending the stomachs with solutions of 5.8% glucose and 8% peptone and by the intravenous administration of histamine. Antibody inhibited responses to glucose and to peptone but not to histamine. BSA=bovine serum albumin, open circles=BSA treated, closed circles=treated with inactive control antibody

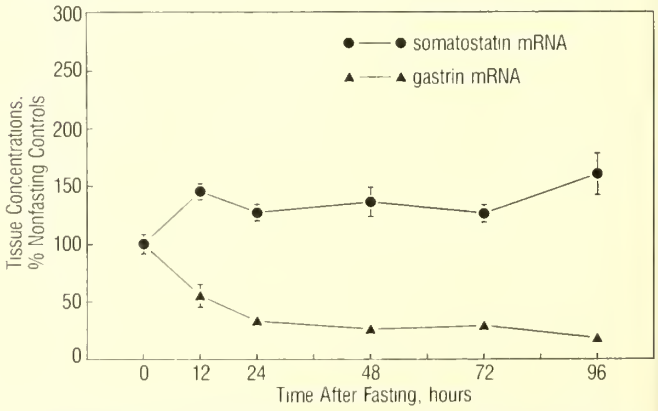

Figure 3.—Gastric antral concentrations of gastrin mRNA and somatostatin mRNA are shown in rats during prolonged fasting with ingestion of water but no nutrients.

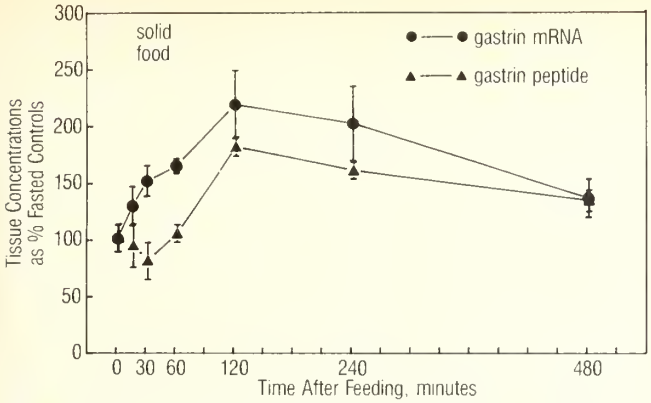

Figure 4.—Gastric antral concentrations of gastrin and gastrin mRNA are shown in rats fed solid chow meal after 48 hours of food deprivation.

Somatostatin monoclonal antibodies reverse this inhibition of acid and gastrin. Urethane causes a selective pronounced increase in somatostatin synthesis in the antrum that does not occur in the acid-secreting portion of the stomach. During urethane anesthesia, the suppressed rate of acid secretion is stimulated by administering a somatostatin monoclonal antibody that reacts with both the large and small forms of somatostatin and is a good in vivo blocking reagent. This stimulation is reversed almost completely by simultaneously administering gastrin monoclonal antibody. We therefore have tools that can be used in animals, but not in people, to manipulate some of the effects of gastric hormones on the stomach.

Trophic Effects of Gastrin

Gastrin is known to be a growth factor for the acid-secreting mucosa. If administered over a long period, gastrin causes gastric mucosa hyperplasia. There also is selective hyperplasia of an endocrine-type cell known as the enterochromaffin-like cell, or ECL cell, found only in the mucosa of an acid-secreting stomach. These cells are responsive to both exogenous and endogenous gastrin. When gastrin was infused into rats at different doses for one month with minipumps, the ECL cell number increased when serum gastrin concentrations were increased in the range of 1,000 pg per ml (476 pmol per liter).

Administering strong acid-reducing drugs such as omeprazole for the lifetime of rats (two years) leads not only to a proliferation of ECL cells but also to ECL carcinoid tumor formation. Hyperplasia of ECL cells and gastric carcinoid tumors have been produced by several potent antisecretory agents administered long term to rats. The common factor appears to be drug-induced hypergastrinemia. Similar results were obtained when the acid-secreting stomach was almost completely resected. In rats left with only a tiny remnant of acid-secreting mucosa, insufficient to acidify the lumen, the same type of ECL cell hyperplasia and tumor formation occurs. These ECL cell carcinoid tumors may invade locally, but they rarely metastasize outside the stomach in rats. The so-called gastrin hypothesis, that carcinoids are due to hypochlorhydria leading to hypergastrinemia, is supported by the finding that this sequence of ECL cell hyperplasia and tumor formation is prevented by resecting the antrum.

Relevance to Human Hypergastrinemia

It has been well shown that omeprazole and other acid-inhibiting drugs can cause increased serum gastrin responses to food and increased basal gastrin concentrations in humans. In a study carried out at the UCLA School of Medicine, omeprazole given for four weeks at doses of 20 to 40 mg per day caused increased average peak gastrin values as high as 100 to 200 pg per ml (48 to 95 pmol per liter). To put this in perspective, the natural model for hypergastrinemia in humans is pernicious anemia. The average serum gastrin values in these patients often are more than five times those induced by potent antisecretory drugs. In pernicious anemia, ECL cell carcinoid tumors and hyperplasia of the ECL cells in the stomach have been closely correlated with serum gastrin concentrations. The degree of ECL hyperplasia found in these patients is paralleled by increased mean serum gastrin levels, and carcinoid tumors are rare in patients with serum gastrin levels of less than 1,000 pg per ml. It has been predicted that ECL carcinoid tumors will develop in as many as 4% to 5% of patients with pernicious anemia. In Zollinger-Ellison syndrome in which there is hypersecretion of acid, along with pronounced hypergastrinemia, ECL carcinoid tumors are found occasionally. As yet, following vagotomy or the use of omeprazole, this sequence of ECL cell hyperplasia and tumor formation has not been observed.

Summary

I have defined some primary and secondary effects of gastrin on the stomach. The secretory effects of gastrin are well known. The trophic effects may be more important than we have previously recognized, particularly with regard to hyperplasia of the ECL cells. I have not discussed the uncertain trophic effects on the colon and the possibility that hypergastrinemia may provoke adenomatous polyp formation or the growth or proliferation of colon cancers. It would be of great interest to develop specific and effective receptor antagonists for gastrin. Such agents could be used experimentally to antagonize the secretory and trophic effects of gastrin. They might also have therapeutic advantage over other antisecretory drugs by combining potent antisecretory activity with antagonism of the trophic effects of secondary hypergastrinemia.

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Articles

Experience With Indeterminate Mammograms

PETER DE NEEF, MD, PhD, *and* JULEANN GANDARA, MD, EdM, *Seattle, Washington*

Most radiologists recommend follow-up mammography in 3 to 6 months for asymptomatic patients with mammographic lesions that do not appear suspicious enough to warrant immediate biopsy. In this retrospective cohort study, the medical records of 776 patients were audited 24 to 35 months after mammography to estimate the frequency of indeterminate lesions, the probability of malignancy, and the rate of patients' compliance with recommendations. Almost 2% of patients retested after an indeterminate mammogram were found to have breast cancer (95% confidence limits 0.2% and 5.9%). Only 26% of the patients retested during the audit period had the test within the suggested upper limit of 6 months. We conclude that timely follow-up after an indeterminate mammogram is advisable and that for the population we studied, compliance with this recommendation is low.

(DeNeef P, Gandara J: Experience with indeterminate mammograms. West J Med 1991 Jan; 154:36-39)

As a result of improvements in image resolution over the past ten years, mammography has become a sensitive test for early breast cancer. Radiologists now can identify subtle signs of cancer, such as microcalcifications or slight distortions in the image of breast parenchyma, that previously could not have been resolved. The mammographic signs of malignant and benign lesions, however, are often not pathognomonic, and the subtle abnormalities that are now identifiable are more likely to be benign than malignant. In this article we report our experience with the follow-up of indeterminate mammograms, where the probability of cancer is low but more assurance is desired.

It would be impractical to do a biopsy of every indeterminate lesion; therefore, when a patient is asymptomatic and the lesion is probably benign, many radiologists recommend a second mammogram in three to six months.[1-3] Although this strategy limits the number of biopsies with negative results, it is a compromise between the optimum management of malignant tumors and nonintervention for benign abnormalities. For malignant lesions, prompt removal is the safest measure. A plan to wait three to six months for more obvious characteristics of cancer to develop in a lesion usually does not affect a patient's prognosis unless the tumor growth rate is high or the patient does not follow up on time.[4-9] For benign lesions, follow-up mammograms do not reduce morbidity or mortality. They do raise patient anxiety, and they increase both the use and the costs of screening programs that face potential shortages of resources.[10-12] Each radiologist's policy for deciding which lesions to follow strikes a balance between opportunities to detect early breast cancers and the expense of additional mammograms for patients who do not have cancer.

In most previous studies relating nonspecific mammographic findings to the probability of cancer, only biopsy results have been used because tissue examination is the gold standard for distinguishing benign from malignant lesions.[13-15] Yet, that approach excludes many indeterminate lesions about which radiologists, referring physicians, and patients must make decisions. In this article we report our experience with mammographically detected lesions for which the suggestion of cancer was initially judged too low to justify a biopsy. We audited patients' records 24 to 35 months after mammography and estimated the frequency of indeterminate lesions, the probability of malignancy, and how often patients comply with recommendations for accelerated follow-up. This report of an outcome assessment of policies at our institution is intended to encourage timely follow-up for patients with indeterminate mammographic lesions.

Methods

Records from the Department of Radiology of the University of Washington Hospital and Clinics, Seattle, Washington, were used to identify a retrospective cohort of patients who had mammograms taken during the seven-month period beginning October 1, 1986. This window of eligibility was selected for three reasons: First, the 24- to 35-month interval between the index mammogram and the chart audit was sufficiently long that most patients had at least one subsequent mammogram or other test to evaluate lesions of interest. Second, all mammograms taken after September 1986 were interpreted by the same radiologist, who specializes in mammography. Third, the mammographic equipment and techniques used at our institution have not changed significantly since then, so the study involves images that meet current standards of quality.

Mammograms are obtained using the Siemens Mammomat dedicated film-screen equipment (Siemens, Munich) with OM single-emulsion film and MIN-R screen (Eastman Kodak, Rochester, NY). All studies consist of a minimum of two views, the 45-degree oblique and the craniocaudal projections. In most cases, films are examined before the patient leaves the facility so that one of the views can be repeated or a coned compression view can be obtained when indicated.

Two experienced chart reviewers with degrees in medical records administration abstracted the relevant radiology, pathology, and clinical reports in patients' charts. Male patients and women with a personal history of breast cancer were excluded. Index mammograms taken during invasive proce-

From the Departments of Family Medicine (Dr DeNeef) and Radiology (Dr Gandara), University of Washington School of Medicine, Seattle.
This research was supported by National Institutes of Health Biomedical Research Support grant No. RR05432.
Reprint requests to Peter DeNeef, MD, PhD, Department of Family Medicine, RF-30, University of Washington, Seattle, WA 98195.

dures were excluded because in those cases recommendations are based on the procedure result rather than on the mammogram. Because their index mammogram report included no recommendation, 19 patients were excluded. Another 15 patients were excluded because they had not received care at our facility during the two years preceding the audit, and their records had therefore been transferred for microfilming. To determine whether including these 15 pateints would have changed the study results significantly, the available records and radiology reports for those patients were reviewed. None had a documented diagnosis of breast cancer. Of the three patients who had indeterminate index mammograms, two had subsequent mammograms that showed no substantial change, and one had no follow-up at our facility.

The indication for each index mammogram was classified as either screening or diagnosis, based on both the requisition completed by the referring physician and a questionnaire administered to each patient in the mammography suite. Screening examinations met all the following criteria: an asymptomatic patient, no personal history of breast cancer, at least 12 months since the last mammogram, and no history of an extensive interventional breast procedure. Although it is common for referring physicians to examine patients before ordering a screening mammogram, some misclassification may have occurred because it was not possible in this retrospective study to ensure that every lesion identified on a screening mammogram was nonpalpable.[16]

For every mammogram report, the radiologist's recommendations were classified in one of three categories:

- Further evaluation is recommended for lesions that appear suspicious or have a high probability of being malignant, and it is also advised when an ultrasound study or needle aspiration is likely to assist the diagnosis.
- Follow-up mammography within three to six months is recommended for patients with indeterminate mammograms in which a lesion is probably benign but further assurance is sought. Mammographic findings for which follow-up is advised include these newly seen lesions with benign characteristics: a group of five or fewer calcifications, a well-defined round or oval mass less than 1 cm in diameter, and a moderate or large asymmetry in tissue density. In a few cases, the radiologist recommends the alternative of further evaluation or follow-up mammography. Those mammograms were also classified indeterminate.
- Routine screening mammography is recommended for the remaining patients.

For the purposes of our study, a lesion was regarded as benign if a subsequent mammogram resulted in the recommendation of routine screening mammography in one or more years, an aspiration or biopsy result was consistent with a benign lesion, or an ultrasound study showed a simple cyst.

The ranges of uncertainty for estimated probabilities of cancer are the 95% confidence intervals of the binomial distribution.

Results

Of the 776 patients who met the eligibility criteria, 482 had the index mammogram for screening, and 294 had the mammogram because of symptoms reported by the patient, a physical finding by her physician, or a previously seen lesion. Table 1 shows the age distribution of the 776 patients at the time of the index mammogram. The mean age of screened patients is 52.7 years (standard deviation [SD] = 13.1). The mean age of the patients who had diagnostic mammograms is 48.2 years (SD = 14.4).

The last column in Table 2 lists the total number of patients with each recommendation in the written report for the index mammogram. The numbers of patients with screening as the indication for the test are included in the totals and are displayed separately in parentheses. Table 2 shows that of the 776 patients, 172 (22%) were advised to have a follow-up mammogram in three to six months. Of the 482 screened patients, 105 (also 22%) had indeterminate mammograms.

The mean age of patients in each recommendation category is about the same. When patients with screening mammograms are analyzed separately, the mean ages in each of the three recommendation categories are all within 1.4 years of the mean age, 52.7 years, of all screened patients. When patients with diagnostic mammograms are analyzed separately, the mean ages in the three categories are all within 1.1 years of the mean age, 48.2 years, of that group.

The other columns in Table 2 show the outcomes of follow-up testing. For example, 12 patients (6 of whom had screening mammograms) were advised to have further evaluation, but their medical records did not indicate that they did so. Of those advised to have further evaluation, nine patients had subsequent mammography instead, and the diagnosis

TABLE 1.—*Age Distribution of the Study Population (n=776) Arranged by Indication for the Index Mammogram*

Age, years	Patients, No. Diagnostic Mammogram	Patients, No. Screening Mammogram
20 to 29	27	1
30 to 39	59	81
40 to 49	88	143
50 to 59	53	106
60 to 69	40	90
70 to 79	22	52
80 to 89	4	9
90 to 99	1	0
Total	294	482

TABLE 2.—*Number of Patients With Each Outcome, Grouped From the Index Mammogram**

Recommendation	No Further Tests	Unresolved Follow-up	No Evidence of Disease	Malignancy	Totals
Evaluate	12 (6)	9 (3)	55 (18)	9 (4)	85 (31)
Accelerated follow-up	37 (22)	14 (10)	119 (72)	2 (1)	172 (105)
Routine follow-up	282 (194)	10 (5)	224 (146)	3 (1)	519 (346)
Total	331 (222)	33 (18)	398 (236)	14 (6)	776 (482)

*Screened patients are included in the numbers and displayed separately in parentheses.

was unresolved. Of another nine patients for whom evaluation was recommended and who were found to have breast cancer, seven (including 3 screened patients) had infiltrating breast carcinoma and two (including 1 screened patient) had carcinoma in situ. Of the patients with infiltrating carcinoma, four (including all 3 screened patients) had stage I disease, two had stage II involvement, and one had widespread metastasis.

Of those with indeterminate mammograms, two patients had malignant disease: One patient advised to have accelerated follow-up because of calcifications seen on a screening mammogram did not return until 11 months later, when she had multiple bony metastases from breast carcinoma. The other patient's index mammogram was indeterminate because of an area of asymmetry that corresponded to a palpable breast lump. A biopsy of the lesion was done, and it was found to be lobular carcinoma in situ.

Of the three patients for whom routine screening was recommended and who were later found to have breast cancer, two (including 1 screened patient) had carcinoma in situ in areas where benign-appearing lesions were noted in the index mammogram report. It is possible that the benign-appearing lesions were coincidental findings. Infiltrating ductal adenocarcinoma developed in the third patient, with three of ten lymph nodes showing malignancy. The neoplasm was discovered when a lump was palpated 15 months after the first mammogram. Retrospectively, the index mammogram showed no abnormality at the site where the interval cancer developed.

In Table 3 are listed the reasons why accelerated follow-up was recommended for 172 patients. The most frequent reason is asymmetry, followed by calcifications and a masslike abnormality or density. Data from follow-up tests are available for 121 of these patients (including 73 screened patients). Of these 121 patients, 24 had a biopsy, 5 had a needle aspiration, and 92 had only follow-up mammography. Two of these indeterminate lesions were malignant, so the probability of cancer for this group of patients is 2 of 121, or 0.016 (95% confidence limits 0.002 and 0.059). One indeterminate lesion identified on a screening mammogram was malignant, so the probability of cancer is 1 of 73, or 0.014 (95% confidence limits 0.000 and 0.074).

Patient compliance with recommendations was also audited. By the time of the audit—24 to 35 months after accelerated follow-up was recommended based on a screening mammogram—83 patients (10 + 72 + 1) had a record of some test. Of the 83, only 22 (26%) had the test within six months, the upper limit of the recommended interval. The patient who returned 11 months later with metastatic breast cancer is included in the group of 83 patients. After a year, 18 of the 83 patients (22%) who eventually were retested by the time of the audit had not yet done so. After 18 months, 7 of the 83 (8%) had not yet returned.

Discussion

Deciding whether to do a biopsy of a mammographically detected lesion can be difficult when the findings suggest the lesion is probably benign but further assurance is desired. When a patient is asymptomatic and the lesion does not appear suspicious enough to warrant an immediate biopsy, most radiologists recommend follow-up mammography in three to six months.[1-3] In this article we report our experience with follow-up of these indeterminate mammograms.

TABLE 3.—*Reasons for Recommending Accelerated Follow-up for 172 Patients*

	Patients, No.		
Abnormality	*Diagnostic Mammogram*	*Screening Mammogram*	*Total*
Asymmetry	21	44	65
Calcifications	18	22	40
Calcifications plus other	6	6	12
Masslike or density	15	24	39
Asymmetry plus density	7	7	14
Skin irregularity	0	2	2
Total	67	105	172

Any policy to follow some lesions and to do a biopsy of others produces a trade-off among patients with early breast cancers detected, those with negative biopsy results, and the use of additional mammograms for patients who do not have breast cancer. Accelerated mammographic follow-up was recommended for 22% of the patients in this study. Between 1% and 2% of those retested had breast cancer. In two recent articles the opinion was expressed that follow-up is acceptable when the probability of malignancy is in this range.[3,7]

Policies for recommending biopsy and accelerated follow-up differ among radiologists. Cyrlak quotes widely varying positive or inconclusive "call rates" in screening programs.[11] Depending on the facility, from 5% to 35% of screened patients were recommended for additional evaluation at 12 participating mammography centers. These figures include calls for additional views, physical examinations, ultrasonograms, and accelerated follow-up and are therefore not directly comparable with the estimates reported here. They are evidence that a wide range of policies was used by the radiologists who participated in one screening program.

The growth rate of breast cancer can differ considerably from one patient to the next,[4,5] and opinions vary regarding the optimum interval for follow-up mammography.[1] Some radiologists recommend reimaging in about three months for women aged 40 to 49 and six months for older women.[17] Recognizing that it is unusual to detect growth after only three months, other radiologists usually recommend follow-up after four to six months.

A commonly measured characteristic of screening programs is the malignant biopsy rate, which is the number of biopsies showing malignancy divided by the total number of biopsies done. For nonpalpable breast lesions, the malignant biopsy rates reported in the literature range from 11% to 36%.[7,11,14] The rate for screened patients in this study is 6 of 35 (17%), and for all biopsies it is 14 of 87 (16%). These rates are at the low end of the published range, a finding consistent with the expressed policy at our facility in favor of the aggressive diagnosis of early breast cancer.

The frequency of indeterminate mammograms is less commonly reported than is the malignant biopsy rate. Brenner and Sickles cite frequencies ranging from 2% to 6% in asymptomatic patients and as great as 20% when a large proportion of the patients are symptomatic.[3] In our study, 22% of asymptomatic patients had indeterminate mammograms, and the rate is the same when symptomatic patients are included.

Wolfe and colleagues report on the follow-up of 21,057 patients, most of whom had breast symptoms.[17] These patients underwent xeroradiography, an alternative to the

method of film-screen mammography used at our facility. The prevalence of cancer in their study population, 0.037, is similar to the prevalence reported here, 0.034 (14 of 412). In the study of Wolfe and co-workers, 6.4% of the patients were recommended to have accelerated follow-up. The probability of malignancy, 0.0074, for indeterminate lesions is also lower than the value 0.016 we measured, but it is within the 95% confidence interval. Evaluations were recommended for 13% of Wolfe and associates' patients, a figure similar to our 11%, whereas the probability of malignancy in that mostly symptomatic group was higher: 0.26 versus 0.14 (9 of 64) in our study.

In most previous studies of nonspecific mammographic findings, only biopsy results have been used because tissue testing is the gold standard for distinguishing benign from malignant lesions.[13-15] That approach excludes many indeterminate lesions that radiologists, referring physicians, and patients must make decisions about. In both the report by Wolfe and co-workers and in our study, lesions are classified as benign if there is no significant change in their image on a subsequent mammogram. Although some breast cancers may be missed by using this criterion, this approach makes it possible to study many lesions that do not appear suspicious enough to warrant biopsy. The audit was carried out 24 to 35 months after the index mammograms to reduce the chance that breast cancers would remain undetected by retesting. If some malignant lesions were not detected with the follow-up mammograms, the actual probability of malignancy is greater than estimated. This would add support to the position that the follow-up of indeterminate mammograms is advisable.

In view of the 1% to 2% chance of malignancy associated with an indeterminate mammogram, the low compliance with recommendations is worrisome. This probability of malignancy is ten times higher than the yearly incidence of cancer in 50-year-old women in the United States (1.7 per 1,000).[12] Of 83 patients who had a follow-up test within 35 months, only 22 (26%) had the test within the recommended limit of 6 months. One patient returned after 11 months with metastatic breast cancer. By one year, 18 patients (22%) had not yet returned for follow-up, and the compliance may actually be worse because these estimates exclude 22 patients who had no record of a subsequent test at our institution.

The possible reasons for low compliance include uncertainty on the part of physicians and patients regarding the risk of cancer associated with an indeterminate mammogram, problems communicating results to patients,[9] and diminished confidence in mammography after an indeterminate result. To the extent that low compliance is due to the lack of data on the risk of cancer after an indeterminate mammogram, outcome studies like this may help to improve follow-up.

The probability of cancer after an indeterminate mammogram depends on the patient population and the policies for selecting lesions for biopsy and for follow-up, so it can be expected to vary among institutions. Studies of patient outcomes after mammography have been advocated for all radiology facilities for medicolegal reasons and for quality assurance.[13,18] Our results suggest another important reason for studies like this: to determine whether patients are receiving the follow-up that has been recommended.

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Articles

Acquired Immunodeficiency Syndrome and Human Immunodeficiency Virus Infection in Nevada

JOSEPH Q. JARVIS, MD, MSPH, *Denver, Colorado, and* SHERRY L. SEMIATIN, *Reno, Nevada*

We summarize information from three sets of epidemiologic data: the Nevada AIDS [acquired immunodeficiency syndrome] Surveillance System, which contains information about every case identified within the state boundaries through September 1989; the human immunodeficiency virus (HIV) seroprevalence reporting systems, which currently include data on all HIV-positive reports submitted statewide to public health authorities; and surveys on the knowledge, attitudes, and behaviors of Nevadans concerning HIV-related disease. The Nevada State AIDS Task Force outlined major policy recommendations, nearly half of which concerned testing; only 2 dealt with preventing HIV transmission. Greater efforts should go into education, particularly directed toward groups at greatest risk of exposure to HIV, and to improve community-based care of infected persons.

(Jarvis JQ, Semiatin SL: Acquired immunodeficiency syndrome and human immunodeficiency virus infection in Nevada. West J Med 1991 Jan; 154:40-42)

Nevada, which has nearly 0.4% of the population of the United States, also has 0.4% of reported cases of the acquired immunodeficiency syndrome (AIDS) in the US. The epidemiologic pattern in the state differs from that in the nation, however. The first cases in Nevada were reported in 1982, two years after the disease was first described elsewhere in the United States. Almost three fourths of Nevada's AIDS cases have been reported since January 1987. Half of the US cases ever diagnosed were reported during that same time period.

AIDS Incidence in Nevada

In the year that ended June 30, 1989, Nevada ranked 7th among the 50 states and the District of Columbia for the incidence of AIDS. As an illustration of the changing AIDS incidence in Nevada over the recent years, Figure 1 compares the AIDS incidence in the US with that in Nevada during the past decade. Both rates are continuing to increase, with Nevada sustaining a steeper rise during recent years than the US as a whole (Centers for Disease Control [CDC], *HIV/AIDS Surveillance* weekly [June 1982 through January 1989] and monthly [February 1989 through June 1989] reports). Substantial increases in AIDS morbidity and mortality will occur in the next few years in Nevada. Not all segments of the Nevada population have been affected equally by the AIDS epidemic. While 60% of Nevadans reside in Clark County (where Las Vegas is located), 72% of all AIDS cases are found there. The majority of cases occur in men aged 20 to 40 (AIDS Surveillance System, Nevada Division of Health, unpublished data, September 1989).

Seroprevalence of Human Immunodeficiency Virus

The prevalence of infection with the human immunodeficiency virus (HIV) is a major determinant of both future AIDS incidence and new HIV infection. A number of seroprevalence studies have been undertaken to quantify the extent of HIV infection in the US population, some of which are also being carried out in Nevada. Since the fall of 1985, all civilians applying for service in the military, including those from Nevada, have been screened for HIV antibodies (CDC, "Quarterly Data Report on HIV in Civilian Applicants for Military Service," written communication, June 1989). The seroprevalence of this group has remained steady or slightly declined over time, being about 0.15% in both the United States and Nevada. Another HIV-seroprevalence study in Nevada involves the unlinked anonymous testing of all newborns for antibody to HIV. Beginning in January 1989, all newborns in Nevada were screened for HIV antibodies. Through the first half year of the screening, fewer than 10,000 specimens had been processed and only 7 were confirmed positive. Nevada is one of few states with a mandatory HIV testing policy for prisoners. Beginning in 1985, all newly incarcerated criminals have been tested for HIV antibody (Table 1). With 13,281 nonduplicated tests done, 262 have been positive, for approximately a 2% positivity rate. This rate has not changed significantly over time.

Beginning July 1988, all laboratories doing HIV testing in Nevada have been required to report positive tests by age, sex, and county of residence. In all, 737 new HIV seroconversions were reported during the first year, which is not necessarily an unduplicated count. An additional 100 seroconversions are reported each year from anonymous test sites in public health clinics throughout the state. Taken together, these statistics seem to indicate that Nevada is experiencing nearly a thousand new HIV infections each year.

Prevalence of Knowledge, Attitudes, and Behaviors Related to HIV

The rapidity of the spread of HIV infection depends on the prevalence of the infection and of behaviors known to transmit the virus. Data about the prevalence of these behaviors among Nevadans as well as their knowledge and atti-

From the Medical Programs (Dr Jarvis) and the Office of Rural Health (Ms Semiatin), University of Nevada School of Medicine, Reno. Dr Jarvis is currently with the Occupational Medicine Program, National Jewish Center, Denver, Colorado.

Reprint requests to Joseph Q. Jarvis, MD, Occupational Medicine Program, National Jewish Center, 1400 Jackson St, Denver, CO 80206.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
HIV = human immunodeficiency virus

tudes about AIDS have been collected by the three public health agencies in the state (the Nevada Division of Health, the Washoe County District Health Department, and the Clark County District Health Department). Multiple groups were surveyed, such as persons attending sexually transmitted disease clinics; clients of the Women, Infants, and Children Food Program; clients of drug treatment programs; patients in family planning clinics; and some high school students. Because the sample was not randomly selected, the survey results cannot be considered representative of Nevadans. Of 2,600 people surveyed, about 80% were female; 60% were between the ages of 20 and 29. Recognizing these biases, the following points can be made:

- Misinformation about AIDS continues to trouble many of those surveyed. Only half the respondents knew that chickenpox is transmitted more easily than HIV and that mosquitoes do not transmit HIV. One in four thought that donating blood would put them at risk for HIV infection.
- The vast majority did not feel that they had had exposure to HIV, yet a quarter of them had had themselves tested for HIV antibodies. As many as 40% of the respondents were unsure what a positive HIV antibody test means.
- Most respondents described themselves as having changed personal behaviors in response to the AIDS epidemic.
- Nearly all respondents would want to be told if one of their sexual partners had a positive HIV test.
- Condom use is greatest among respondents with multiple sexual partners, but only a third of those with two or more partners describe regular use.
- Most respondents relied on radio and television for whatever AIDS information they receive.

HIV Policy in Nevada

Summaries of epidemiologic data concerning the Nevada HIV epidemic were published by the Nevada AIDS Task Force in 1987 and 1988. The state AIDS Task Force has made 41 recommendations to the Governor and the Nevada State Board of Health.[1] Of these recommendations, 19 concern HIV testing, 14 designate the state agencies needing HIV policies, and 6 concern HIV training or counseling. The remaining 2 recommendations are specifically preventive in scope. Given the steady increase of AIDS incidence and the apparent ongoing spread of HIV infection, it will be important for the state AIDS Task Force to go beyond these initial recommendations toward more definitive statements about reducing HIV morbidity and mortality in Nevada. Possible policy considerations include the following:

- Focus less on who should be tested for HIV and more on who should be educated about HIV. The behavior surveys in Nevada indicate that often the people who have been tested do not understand test results, nor do they possess good information about HIV-related diseases. Mandatory testing is expensive and adversarial in nature and not conducive to learning or behavior modification. Persons and communities are more likely to act appropriately when informed than when ordered.
- Focus intensive, substantive AIDS education outreach on groups most in need. In Nevada, men who have sex with other men continue to compose the majority of AIDS cases and to have the highest HIV seroprevalence. Efforts to assist gay communities elsewhere to build a social norm of abstinence or safer sex practices have been effective and should be organized in Nevada. A second group needing intensive AIDS education outreach are college-age Nevadans. The number of AIDS cases diagnosed before age 30 and the measurable prevalence of HIV antibodies in military recruits indicate that the college-age population is at increased risk for HIV transmission. These and perhaps other groups of Nevadans need more than radio and television information.
- Plans should be made to contact and counsel every Nevadan known to have exposure to HIV. Almost all respondents to the knowledge, attitude, and behavior survey indicated that they would prefer to be informed if their sexual contact was or became HIV-positive. Objections to partner notification have been based on cost, efficacy of treatment, and discrimination.[2] Published estimates of costs for partner notification place the price within reach of current nationwide funding. In Nevada, as few as ten additional case workers would be able to handle most if not all needed partner notification. Personal contact with counseling, because it discourages the denial of risk and encourages healthy behavior, may be the most effective treatment of persons with

TABLE 1.—*HIV Mandatory Testing in Nevada Prisons, 1985 to July 1989*

Year	Total Tested, No.	Total Positive, No.
1985	4,750	95
1986	2,210	44
1987	2,103	42
1988	2,603	52
1989	1,615	29
	13,281	262

HIV = human immunodeficiency virus

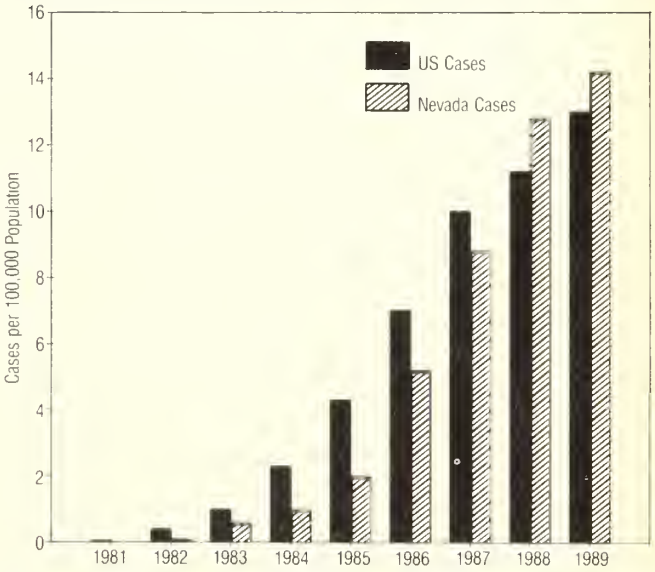

Figure 1.—The graph shows the estimated US and Nevada AIDS incidence rates for 1981 to July 1989 (from Centers for Disease Control *HIV/AIDS Surveillance* reports).

known HIV exposure. Statutory protection of public health records exists in Nevada, increasing the likelihood of confidentiality for reports.[3]

• Finally, the increasing number of persons with AIDS and the earlier identification of asymptomatic HIV-infected people must be addressed with organized community-based care for HIV morbidity. Advances in clinical medicine, such as delineating the biologic markers of disease progression and improvements in antiviral therapy and in the control of opportunistic infections, have enabled the medical community to offer effective early intervention to HIV-infected patients.[4] In addition to improved health for HIV-infected patients, organized early intervention offers the best opportunity for preventing the spread of infection.

All of these proposals cost money. The federal government is currently spending at least $1 billion annually on AIDS prevention and research, but not all states are equal partners in this expense. Nevada, ranking 7th in the AIDS incidence, ranked 24th among states for per capita state health agency AIDS expenditures budgeted for 1989 (*Public Health Macroview,* January/February 1989; 2:5). Consideration should be given to increasing state expenditures for the control of HIV-related morbidity and mortality in Nevada.

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BYPASS

They have taken pieces of your leg vein
And done what they can. Walking
On your land, you laugh: "We don't think
Of the heart as well protected" and thump
The ribs they had to break
Explaining how you'd been suffocating
For the past year, living on less
And less oxygen. Giddy with delight
You spread your arm to the shagbark hickories
That lean near stone fences. "I'm blessed
And I didn't know it 'til this;
I've work I love, family and friends,
Even my parents, getting on, are still alive."
You think you came to at one point,
Saw an instrument leaning
From the open cavity, a *trocar,*
"Can you imagine?" and describe
A tool for torture, instead of repair.
When you saw the red tracks of stitched skin
As if it were fabric to be pinched and sewn,
You say you spoke to yourself aloud:
"I'm still alive! Amazing!"
Now you've become devout, cherish
What's unseen and the smallest of animate things,
A piece of gray hickory bark that's come
Away on your hand, a dead scale of skin.

DONA LUONGO STEIN
Aptos, California

Surplus or Shortage?
Unraveling the Physician Supply Conundrum

ROGER A. ROSENBLATT, MD, MPH, *and* DENISE M. LISHNER, MSW, *Seattle, Washington*

Although the supply of physicians in the United States has doubled during the past 20 years, there is still disagreement as to whether we currently have or should expect a significant surplus of physicians. The evidence suggests that despite the rapid expansion in the pool of available physicians, serious physician shortages persist for certain rural populations, ethnic and occupational groups, and other medically disadvantaged segments of the population. Medical students' declining interest in rural practice and primary care specialties suggests that problems of geographic and specialty maldistribution may worsen despite a rising population of physicians. It is unlikely that a significant physician surplus will develop unless there is a conscious attempt to limit the proportion of national wealth expended on medical care. Pockets of shortage can be reduced by broadening the availability of health insurance, lessening large income disparities between different specialties, changing the way teaching institutions are reimbursed for their training costs, and supporting direct governmental service programs such as the National Health Service Corps.

(Rosenblatt RA, Lishner DM: Surplus or shortage?—Unraveling the physician supply conundrum. West J Med 1991 Jan; 154:43-50)

The production of physicians should be increased beyond presently planned levels by a substantial expansion in the capacity of existing medical schools and by continued development of new schools.

The Report of the National Advisory Commission on Health Manpower, 1967[1]

If medical school expansion is financed in order to create more doctors because some persons are without sufficient physicians' services, then it must be recognized that additional personnel will not necessarily make those services available to those very people.

RASHI FEIN
The Doctor Shortage: An Economic Diagnosis, 1967[2]

There will be too many physicians in 1990. There will be substantial imbalances in some specialties. There will continue to be a marked unevenness in the geographic distribution of physicians. (Emphases deleted.)

Summary Report of the Graduate Medical Education National Advisory Committee to the Secretary of Health and Human Services, 1980[3]

How many physicians does the United States need? The question is simple, but the answer is convoluted and controversial. Despite the plethora of studies that explore the issue of physician supply, different authors often arrive at different conclusions not only about how many physicians are needed, but on what policies should be adopted to ensure an adequate and appropriate number and mix of physicians in the future.

In this article we review the current debate about physician resources in an attempt to reconcile the widely divergent viewpoints about the number and type of physicians required by the United States. The underlying thesis of this discussion is that the question cannot be asked in a conceptual vacuum. To determine how many physicians should be trained in specific specialties, the dimensions of the health care system we are attempting to achieve must first be specified. The major source of controversy in the field of physician supply forecasting is a lack of agreement over the shape of an optimal health care system. This confusion is further compounded by the fact that the US health care system is in perpetual flux, which constantly modifies both the demand and the supply sides of the health professional forecasting equations.

Despite the lack of a firm foundation, it is possible to clarify the major alternatives available as this century wanes. To put the competing policy recommendations into some sort of reasonable conceptual context, we will attempt the following:

- Discuss the methodologic approaches that have been used to determine physician work-force needs and summarize the key projections of the major studies done in the past 30 years;
- Specify the competing assumptions about how the health care system should be constructed that lead to diverse recommendations about future attempts to shape physician supply;
- Examine some of the areas of present and future change that may modify any forecasts of physician supply or demand; and
- Offer some specific suggestions about further policy development in this field.

Physician Supply Forecasting—Science or Voodoo?

In theory, it should be simple to determine whether there are enough physicians. Two variables must be quantified: the need for physicians and the supply of physicians. A surplus exists when the supply exceeds the need; a shortage is the converse.

In fact, all work-force studies proceed from this conceptual framework. Unfortunately, it is often difficult to quantify

From the Department of Family Medicine, University of Washington School of Medicine, Seattle.

Reprint requests to Roger A. Rosenblatt, MD, MPH, Professor and Vice Chair, Department of Family Medicine, Research Section HQ-30, University of Washington, Seattle, WA 98195.

ABBREVIATIONS USED IN TEXT

COGME = Council on Graduate Medical Education
GMENAC = Graduate Medical Education National Advisory Committee
HMO = health maintenance organization
NHSC = National Health Service Corps

the variables in the human resources equation. Although it is relatively straightforward to count physicians, all physicians are not equal with respect to the amount of time they work, their relative productivity, or the value of the services they produce. How should the contribution of residents be weighted relative to that of physicians in practice for 20 years? Are women physicians more likely than male physicians to work part time? Do surgeons in health maintenance organizations work as hard as their peers in the fee-for-service sector?

The complexity of estimating physician supply pales in comparison with the much thornier problem of determining need. While the supply side of the equation poses substantial technical problems, the issue of need or demand raises both important methodologic and philosophical issues.

Two basic approaches have been developed to answer the question of how many physicians are required. The more straightforward of the two is the demand-based approach, which proceeds from some measure of the current level of use as the norm and adjusts for changes in population. The fallacy embedded in this approach is the explicit assumption that the current use patterns and levels are appropriate. The demand-based method, while conceptually simple, can be technically complex.

The competing paradigm is the needs-based approach, a normative model that calculates physician requirements based on an idealized determination of the volume of health services that a population would receive in the best of all possible worlds. Such an approach was used in one of the earliest comprehensive physician resource studies. In this ambitious effort, the consensus of a panel of experts was used to develop an estimate of the number of physician hours required to prevent, diagnose, or treat the range of conditions seen in a normal population.[4] The more recent study of the Graduate Medical Education National Advisory Committee (GMENAC) is in fact a variation on the needs-based model, and expert consensus panels and a modified delphic approach were used extensively in generating GMENAC's estimates of how many physicians are required.[5]

Table 1 is a summary of the structure, methods, and principal conclusions of selected major physician resource studies done over the past 60 years, spanning an era that opened with the classic work of Lee and Jones and ended with the report of the Council on Graduate Medical Education (COGME).[3,4,6-10] As the table shows, the federal government has sponsored most of the major studies in this field. At the risk of oversimplifying, the 20th century can be conveniently divided into eras of physician shortage and of surplus, with the 1980 GMENAC report demarcating the watershed. Before 1980, the conventional wisdom proclaimed significant physician shortages, and this conclusion triggered a wide variety of public interventions, including the creation of new medical schools and a major expansion of medical school classes.[11] The GMENAC's main conclusion was that this fusillade of intervention had overshot the mark, transforming President Lyndon B. Johnson's 1968 proclamation of a shortage of 50,000 physicians[12] into a projected surplus of 70,000 physicians by the year 1990.

Whatever its methodologic shortcomings, the GMENAC study did not mince words. In calling for an immediate 17% reduction in medical school class size and for the severe restriction of the entry of foreign medical graduates into the United States, GMENAC threw down the policy gauntlet. The GMENAC report was readily embraced by a new administration eager to distance itself from the interventionist policies of its predecessors. As a consequence, many federal programs designed to influence physician supply or distribution were scaled back, and the federal government turned its immediate attention from problems of health care access to the more pressing problem of cost.

Yet all was not quiet on the physician resources front. The GMENAC study spawned the creation of a thriving cottage industry whose main product was research pointing out substantial errors or oversights in the committee's report. Some found the projected physician surplus illusory,[13] but others proclaimed the prediction of physician surplus too timid.[14]

TABLE 1.—*Selected Studies of Physician Supply in the United States, 1933-1988*

Authors and Year Published	*Sponsoring Organization*	*Methodologic Approach*	*Major Conclusions*
Lee and Jones, 1933[4]	Committee on the Costs of Medical Care	Need based; consensus of experts as to physician hours required to treat specific diseases	National shortage of physicians
President's Commission on the Health Needs of the Nation, 1953[6]	Presidential commission	Demand model based on optimal population-physician ratios	Substantial national shortage of physicians
Bane Committee, 1959[7]	US Surgeon General	Demand model; postulated a minimum of 141 physicians per 100,000 population	Persistent national physician shortage
GMENAC, 1980[3]	DHEW	Adjusted-needs model; expert panel consensus on individual diseases adjusted for fraction of diseases treated by physicians	Impending severe physician surplus in most medical and surgical subspecialties
COGME, 1988[8]	DHHS	Public hearings, expert testimony, secondary data analysis	Probable physician surplus of unknown magnitude; persistent problems of geographic and specialty maldistribution
Bureau of Health Professions, 1988[9]	DHHS	Adjusted-demand model	Significant physician surplus (70,000 by year 2000)
American Medical Association (AMA), 1988[10]	AMA	Adjusted-demand model	No conclusion

COGME = Council of Graduate Medical Education; DHEW = US Department of Health, Education, and Welfare; DHHS = US Department of Health and Human Services; GMENAC = Graduate Medical Education Advisory Committee

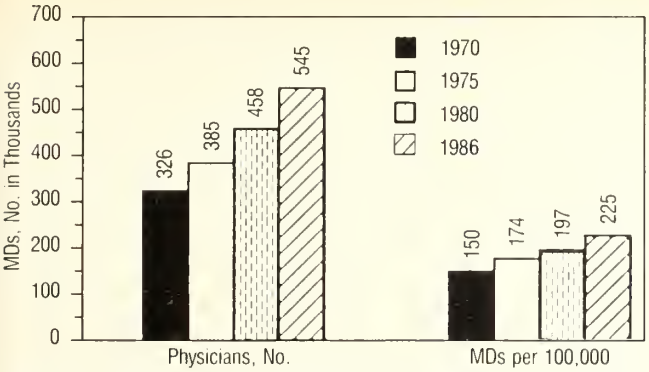

Figure 1.—The graph shows the increase in the absolute and relative supply of allopathic physicians in the United States, 1970 to 1986.

Thus it is not surprising to find that the most recent governmental pronouncement on this issue, the first report of the Council on Graduate Medical Education, is a model of vacillation.[8] Although COGME concludes that there is likely to be an aggregate oversupply of physicians, this conclusion is draped in uncertainty. The COGME recommendation is as tentative as GMENAC's was forthright: "At the present time, the Federal Government should not attempt to influence physician manpower policy in the aggregate."[8]

Despite the lack of consensus on the adequacy of America's physician supply, the basic statistics are not in doubt, as can be seen in Figure 1. The number of medical schools increased from 87 to 126 between 1963 and 1980, and the number of medical graduates more than doubled during that same period. As a consequence, the relative supply of physicians has risen from 150 per 100,000 in 1970 to 225 per 100,000 in 1986.[15] At the same time, more Americans lack basic access to health care, both the absolute and relative supply of physicians in some rural areas has decreased, and many defined population groups have more difficulty gaining access to physicians. National physician resource policy is not about physician numbers only.

How Many Doctors Can Fit on the Head of a Pin? It Depends on the Shape of the Pin

The major source of disagreement about the adequacy of America's physician supply is substantial controversy about what constitutes an optimal health care system. Perhaps the best way to illustrate this proposition is to briefly review the approaches of two respected analysts with diametrically opposed views on this issue.

William Schwartz and co-workers have been the most provocative exponents of the contrary notion that we are more likely to face a physician shortage than a surplus by the year 2000.[13] They find many reasons to take issue with the assumptions on which GMENAC and others based their projections, but their main argument is based on the fact that the demand for medical services can be expected to continue to increase at a relatively rapid rate. The aging of the population, the advent of new diseases such as the acquired immunodeficiency syndrome, and, most important, the increasing array of technically sophisticated medical services that will be available will require more physicians. At the same time, these observers expect that more physicians will be siphoned off into non-patient care activities, largely administration and research, and that the productivity of the rest will actually decrease. Although Schwartz and colleagues concede that their model is subject to the vagaries of reimbursement policies and the unpredictable nature of technologic innovation, their analysis is a direct attack on the GMENAC approach and conclusions.

At the opposite end of the spectrum are those who observe that managed systems of health care—exemplified by the health maintenance organization (HMO)—use substantially fewer physicians than does the private sector. Steinwachs and associates point out that HMOs typically use 20% to 50% fewer physicians to care for children and adults, respectively.[14] Tarlov uses this and other observations to argue that as the number of persons who become part of managed care organizations increases, projections for the increasing dominance of this "third compartment" of medical care will need to be adjusted.[16] A typical HMO has a staffing level of about 120 physicians per 100,000 population, only about half of that in the "first compartment" or fee-for-service sector and much lower than the physician-population ratio projected for the 21st century.[17]

The roots of this disparity are diametrically opposed visions of what constitutes an optimal health care system. Schwartz and co-workers anticipate the further development of a highly specialized health care system in which well-trained subspecialists basically make beneficial technologies available to the population at large. In this system, subspecialists will diffuse from the academic centers into most cities of more than 50,000, and health insurance will expand to make consumers able to purchase the services purveyed by these subspecialists.[18] Tarlov, by contrast, predicts the evolution of a tightly managed system of care in which costs are contained and where most care is provided by primary care physicians.[16]

The consequences of these differing assumptions about what the medical care system will look like are of a much greater magnitude than are the uncertainties introduced by such vagaries as the productivity of women or immigration policies for foreign medical graduates. The "third-compartment" model described by Tarlov can probably be adequately staffed by 120 physicians per 100,000 persons, whereas Schwartz and colleagues' vision of the future of medicine would comfortably employ more than twice that number. Given that the proportion of Americans who receive their medical care from managed health care organizations is likely to increase and that the quality of care in those settings appears similar to that available in the traditional fee-for-service sector, the added value provided by the additional 300,000 physicians required in an unfettered fee-for-service model should be questioned.[19-21]

Sources of Uncertainty: Vexing Issues in the Physician Work-force Debate

Human resource forecasting is part of a larger social dialectic. Authoritative predictions of physician shortage or surplus almost inevitably set in motion educational and social changes that start the pendulum swinging in the opposite direction. The physician shortages of the 1960s led to the governmental interventions that created the physician surplus of the 1980s.[22] It is not too surprising that in the decade that has followed, there have been a restriction on foreign medical graduates entering this country, a modest contraction of some medical school classes, and a reduction in the extent to which government employs and deploys physicians.[23] The pendulum does not swing; it is pushed.

This constant recalibration of the system by which physicians are educated and licensed at least partially invalidates the basic assumptions of any specific forecasting model soon after it is published. In addition to these deliberate attempts to modify physician supply, other simultaneous social phenomena affect the attractiveness of medicine as a profession, the kind of people who choose to enter medicine, and the work habits of physicians. Perhaps most important, the aggregate physician supply is only one factor that determines whether or not certain large and important segments of the population have access to medical care. In the following section, we discuss some aspects of both the health care delivery system and the educational system that must be considered in any comprehensive discussion of physician supply policy.

The Applicant Pool

The number of medical students in the United States doubled in the past 25 years, from 7,081 in 1960 to 16,318 in 1985.[15] Although the number of applicants to medical school rose commensurately until 1973, the applicant pool actually declined until leveling out in 1990.[24] The consequence has been a decline in the applicant-to-acceptance ratio and a shift in the composition, quality, and values of the applicant pool.[25]

Although many explanations have been proffered for this decline in the number of persons interested in becoming physicians—from the falling status of physicians in society to the increasing expense of acquiring a medical education—the result is a smaller roster of persons to choose from. This may ultimately hasten the decisions of some of the more marginal medical schools to reduce class size or get out of the business of medical education altogether. Of equal or greater significance is that all medical schools will have more difficulty selecting incoming classes suitable to the social and intellectual mission of the medical school. As more entering students seek lucrative subspecialty careers in urban settings, schools interested in fostering rural practice or primary care may find it more difficult to achieve those objectives.

Women Physicians

The most dramatic change in the demographic composition of new physicians is the growing number of women.[26,27] As the number of male applicants fell, the absolute number and relative proportion of women in the applicant pool quadrupled. More than a third of current medical school applicants are women, and it is expected that by the year 2010 almost a third of all physicians will be women.[28,29]

This transformation of the medical profession from a male-dominated club to one in which women are equal partners has implications beyond merely expanding day-care opportunities for residents and their children.[30] Women are more likely to work in salaried settings and to work fewer hours than men, although the differences are decreasing. Women are also less likely to settle in rural areas, and they show a predilection for certain specialties. This changing demographic profile of the medical profession will tend to reduce the effective physician work force, although the magnitude of the difference is small. The growing proportion of women may also exacerbate the problem of physician maldistribution. The most pervasive effect is likely to be an augmentation of the preference of recent graduates to join salaried practices in structured settings where the work conditions are at least as important as the wage.

Minority Physicians

Minorities have been consistently underrepresented among American physicians.[31] In 1985, only 3% of US physicians were African American at a time when about 12% of this country's population was in this racial group.[32] If we accept the premise that the proportion of minorities in medicine should reflect their distribution in the general population, there is a severe shortage of minority-group physicians. The evidence that these physicians are more likely to provide primary care services to underserved minority populations is a strong reason to embrace such a staffing goal.[32]

The widespread perception of a physician surplus has undermined recent efforts to expand the number of minorities in medicine. The federal government's decision to cut back on financial assistance to medical students at a time of rising tuitions disproportionately affects minorities because they frequently come from poorer families.[33] As opportunities for minorities expand in other professions, and as the debt burden for medical school graduates increases, many capable potential applicants will choose other fields. Although this will have only a marginal effect on the overall applicant pool, this lack of investment in training minority physicians may ultimately reduce our ability to rectify disparities in the supply of health services to underserved minority populations.

Foreign Medical Graduates

The foreign medical graduate is a persistent wild card in the debate about physician-supply policy. In the mid-1960s, physician immigration was encouraged as a step toward alleviating the perceived physician shortage, and foreign nationals trained abroad were actually given preferential entry into the United States.[34] When the consensus concluded that the physician supply had overshot the desired mark, occupational preference was restricted. Subsequently, examination requirements have been made more rigorous, further restricting the influx of foreign medical graduates.[35] The general sentiment is that in an era of homegrown surplus, we need not depend on foreign graduates.

The contribution of foreign medical graduates to the supply of US physicians is not inconsequential; in 1983, well over 100,000 foreign graduates were practicing in this country, accounting for more than a fifth of the total physician supply.[36] If it were possible or desirable to eliminate foreign-trained physicians in this country, the supply of physicians would be constrained appreciably; it may be neither possible nor desirable, however. Most foreign medical graduates now enter the United States as US citizens, and it may be neither politically feasible nor fair to exclude them from the practice of medicine.[37] In addition, foreign-trained physicians from all countries show both tenacity and ingenuity in gaining a foothold in the United States, circumventing the immigration restrictions and transcending the more difficult licensing barriers.[34] Without much more draconian legislation, the tide is unlikely to ebb. Furthermore, like new immigrants in other fields, foreign medical graduates are willing and even eager to take the jobs that the homegrown product shuns. They disproportionately staff both inner-city emergency departments and isolated rural clinics, and even if the flow could be

stemmed, it might do little to ameliorate any surplus of physicians in areas that are already well served.[35]

Geographic Maldistribution

Even as GMENAC proclaimed the impending physician glut, the committee emphasized that substantial physician shortages persisted, with the most obvious deficiencies in rural areas of America. Physicians are not uniformly distributed across the country.[3] In fact, there is a tenfold difference in the physician supply of urban and rural areas, a relative disparity that persists despite the expansion of the total number of practicing physicians. Although there has been a modest increase in the number of physicians practicing in larger rural communities, many of the most isolated communities continue to be underserved altogether.[38]

The persistent plight of rural communities has historically been a major force behind the expansion of the physician supply. The policy issue is not whether small towns should have access to physicians, but what steps should be taken to ensure that medical care is available in rural areas. The studies of Newhouse and Schwartz and associates show that the supply of board-certified physicians has increased in many nonmetropolitan areas of the United States, and these authors argue that market forces promote the diffusion of physicians into areas where competition is less.[39,40] On the other hand, numerous studies have shown that physicians have an enormous capacity to create their own markets and to counter competitive pressures by finding new niches in apparently over-doctored urban areas.[19,41-43] Although a diffusion of physicians exists, the deliberate creation of conditions of physician surplus is an extremely inefficient way to ensure that small towns have medical care.

Physicians tend not to choose rural practice for many reasons, perhaps the most important being that rural medicine is hard work at low pay. Many federal and state initiatives instituted in the 1970s sought to address this problem by establishing programs that selected medical students interested in rural life, prepared them appropriately for rural practice, supported them economically in their practice environments, and reduced their isolation with targeted outreach programs based in urban centers.[44-51] Many of these programs were abandoned with the proclamation of a physician surplus, as it became fashionable to cite the inexorable diffusion of physicians into small areas as the "invisible hand" that would remedy any residual shortage of physicians in rural areas.

It seems more sensible to acknowledge that if left to their own devices, physicians will always tend to aggregate in cities. To the extent that it is thought prudent to assure adequate medical care in rural towns, a logical role of government is to pursue redistributive policies that enhance the likelihood that physicians will locate and remain in rural communities. When placed in a larger context, the size of the problem is miniscule. Kindig and Movassaghi point out that the addition of 1,883 physicians in small rural counties would increase the supply of primary care physicians in those settings to that prevailing nationwide.[38] Even if the estimate of deficiency is doubled to make sure that underserved inner-city areas are addressed as well, this means only about 0.5% of physicians in practice today. It is difficult to understand why the decision has not yet been made to solve this problem as a matter of national policy.

Specialty Maldistribution—Whence Primary Care?

Given the choice, most physicians become specialists.[11] The reasons are not difficult to find. Specialists are paid as much as three times more than their generalist colleagues.[52] They enjoy higher prestige, both among their colleagues and from the public at large. The medical schools where they are trained are organized according to specialties and controlled by those who have achieved their leadership positions by demonstrating their prowess in narrow scientific or clinical areas. Our academic health centers are increasingly propelled by and dependent on the fees generated by the specialty departments. And in a world where biomedical knowledge and technologic innovation are rapid and unceasing, many students find it cognitively more appealing to restrict their intellectual domain to an area that they can master in depth.

The clamor for primary care physicians originated outside of medicine, but substantive change has been largely derailed by the medical profession itself, most notably the teaching institutions that control the educational spigots.[53] The flourishing of primary care during the 1970s led to the creation of family medicine as a specialty and to the flowering of general internal medicine as a primary care alternative in the dominant church of American medicine.[54,55] Yet all the primary care workers see themselves in crisis, with educational programs underfunded, residency slots unfilled, and the future uncertain.[56-58]

Perhaps in no other area of physician staffing policy is there greater cognitive dissonance. It is instructive to review the recommendations of COGME in this area:

> There is an undersupply of physicians in family practice. There appears to be an impending undersupply of physicians in general internal medicine. Allopathic and osteopathic medical school graduates should be strongly encouraged to enter training in primary care, particularly in family medicine and general internal medicine.[8(pxxiii)]

"Encouragement" alone will probably have little effect on specialty choice of medical school graduates. This is an area where many of medicine's leaders argue on behalf of primary care, but virtually all of the incentives for persons and institutions favor the production of specialists.

The incentives are powerful, and some are relatively invisible. The direct and indirect medical education support provided by Medicare exceeds $3 billion annually, most going to teaching hospitals to support the training of specialists.[59] By contrast, according to F. Mullan, Director of the Bureau of Health Professions, US Department of Health and Human Services, the total federal grants for family medicine, general internal medicine, and general pediatrics were $55 million in 1989, less than 2% of the amount that flows to hospitals through Medicare subsidies (written communication, July 1989). Specialty residents often generate revenue by helping to staff lucrative inpatient services, whereas primary care residents in the ambulatory setting are expensive to train. It is therefore not surprising that teaching hospitals are supporting the expansion of specialty training at the same time that leaders of academic health centers are decrying the dearth of ambulatory-based education and the lack of interest in primary care.[60] Add to this the billions of dollars a year that flow from the National Institutes of Health to academe for basic research—much of it carried out under the auspices of specialty departments—and the functional inconsequence of primary care to academic medicine is magnified.[61] The hypocrisy is institutionalized.

As in the case of geographic maldistribution, the aggregate supply of physicians has relatively little to do with this debate. The declining interest in primary care among medical school matriculants (from 36% in 1982 to 22.5% in 1989) has occurred in the face of a rapid expansion in the number of practicing physicians[62] and at a time when the effective demand for primary care physicians has been increasing.[63] The core values of both the teaching and practice establishment favor specialization. Unless something is done to change those values or the very real and immediate incentives for physicians to pursue specialty careers, the flourish that primary care enjoyed in the 1970s and early 1980s will be followed by its virtual eclipse.

Other Issues

Many other elements in the staffing discussion cannot be dealt with adequately in this short article but are worthy of brief mention. Discussing the physician work force without touching on the role of osteopathic physicians and allied health personnel is both ethnocentric and myopic. Osteopathic physicians have increased in number even more rapidly than their allopathic peers, with a 90% rise in their number from 1970 to 1986.[9] This group has shown a commitment of graduates to both primary care and rural health care. To the extent that traditional medicine is ineffective in meeting the needs of these underserved population groups, osteopathy can be expected to continue to grow to fill the holes. The rationality of licensing two parallel health professionals with largely overlapping skills and training may be questioned, but those who select osteopathy tend to practice in settings not willingly filled by allopathic physicians.[64,65]

Much of the discussion about physician supply is predicated on a crisp role delineation between physicians and the many other health professionals who provide direct patient services to the public, including nurse practitioners, physician assistants, midwives, and other midlevel and allied health personnel, to say nothing of nontraditional healers such as naturopaths and chiropractors. The mainstream groups grew rapidly during the past two decades, with numeric expansion driven by many of the same concerns that led to the establishment of family medicine programs and other concerns about the paucity of primary care and rural health care providers.[66] As the supply of physicians has expanded, the autonomy and scope of practice of some of these midlevel providers have been constrained, a tendency abetted by the vastly increased demand for nurses in hospitals.[67-69] It should be recognized that there is nothing sacred about the current division of labor and responsibility between physicians and allied health personnel. It has been shown repeatedly that midlevel providers can competently assume many functions traditionally within the purview of physicians.[70] It certainly would be possible to devise a system of care that relied less on physicians and more on health care providers with less formal training.

Discussion and Conclusion

The question of whether there is a significant shortage or surplus of physicians can be answered only in the context of a previous decision about the dimensions of the health care system itself. If the system continues to be basically open-ended, one in which third-party payers facilitate the purchase of new medical interventions as they become available and physicians continue to be able to create a demand for their own services, virtually all physicians in this country will remain gainfully employed.[42,43] Although there may be temporary surpluses of certain physician specialties in certain desirable areas, even in these cases most physicians will find a profitable niche.[41]

If, however, a social contract is created that restrains the growth of the amount or percentage of national income directed to health care, the situation could change rapidly. If resources are limited, society will be forced to allocate a fixed set of resources among competing demands, and an increasingly structured system may render certain types of physicians and their services superfluous. In such a case, it is likely that a substantial number of physicians in the training pipeline would find themselves redundant. The untrammeled nature of private initiative in this country and our notable lack of success in restraining the growth of the health care sector make this scenario unlikely. Even in the context of a nationalized health care system, a vigorous private sector is likely to provide employment for many physicians whose contributions are too costly or too marginal for the more parsimonious public system.

The United States has a persistent health care staffing problem, but it is more than a question of how many physicians to train. More physicians are being trained than at any other point in the history of this country, yet large segments of the population experience a shortage, either because they live where physicians do not choose to practice or because they cannot afford what physicians are selling. It would be sensible to worry less about the aggregate physician supply and more about making the abundant supply of physicians available to persons who need but cannot get medical services.

This review of the many comprehensive studies of the dynamics of the health professionals equation suggests some relatively simple steps that would effectively address the real health care staffing problems of geographic maldistribution, an inadequate number of primary care physicians, and the underrepresentation of minorities. These remedies could include one or more of the following interventions:

- *Create effective demand for underserved populations.* The reason most people go without medical services is that they cannot afford to pay for them. Physicians' services are expensive, and the modalities that they marshal on their patients' behalf are more expensive still. Any universal financing mechanism will allow the poor and uninsured to greatly increase their ability to purchase physician services and will perforce serve a redistributive function as well. To the extent that financing mechanisms allow underserved populations to pay the market price for physician services, physicians will change their practice locations and their patient clientele. Money is the great leveler.
- *Differentially reward providers who practice in "less desirable" areas or care for socially disadvantaged populations.* Physicians tend to cluster in affluent urban areas. Most were raised in those environments or want to raise their children there. This tendency toward centralization is compounded by the concentration of other medical and nonmedical amenities in the major urban areas. To persuade more physicians to settle in rural communities or less well-endowed urban settings, we could pay them more.

This is not a preposterous notion. We currently do just the opposite as a matter of public policy. Rural physicians are

paid lower fees for equivalent services than their urban counterparts by such federal programs as Medicare, and inner-city physicians rely on the relatively meager reimbursement of the Medicaid program for much of their livelihood.[47,53] Physicians can count.[71] If health care professionals are rewarded with some form of bonus for working in areas where they would not otherwise settle, some of the monetary and nonmonetary inducements that now lead most physicians to congregate in the areas where they are least needed could be compensated for.

• *Use governmental inducements to directly affect the specialty and location choices of medical students.* The structure and values of the academic health centers are at the root of the problem of geographic and specialty maldistribution.[72,73] This country's medical schools excel at research and compete effectively in the world of tertiary care but do a mediocre job of teaching and an abysmal job of meeting the needs of primary care and rural physicians. The indictment is not ours; it is borrowed from a self-evaluation exercise indulged in publicly by the leaders of the academic establishment.[60]

It is hardly surprising that academic medical centers are unresponsive to broader societal needs. Full-time faculty members at most medical schools are selected, recognized, and rewarded for their research productivity and clinical prowess. Teaching is an often-neglected by-product of the process of taking care of patients, doing research, and obtaining grants, and most faculty are either indifferent or hostile to such undifferentiated callings as primary care.

What is surprising is that national health policy, despite rhetoric to the contrary, directly subsidizes the current status quo. The National Institutes of Health invest more than $4 billion a year in research at medical schools, and these research funds directly and indirectly subsidize medical education at both the undergraduate and graduate levels. An additional $3 billion goes to teaching hospitals through Medicare's direct and indirect medical care subsidies, flexible funds used primarily to employ specialty residents to assist the hospitals in pursuing their specialty missions. By contrast, the entire grant support for programs for primary care specialties is less than $60 million per year.

Medicare's indirect medical care adjustment is the most powerful tool available for changing the educational emphasis of academic health centers. Rather than passively reimburse these centers for their teaching programs, it would be possible to reward those hospitals whose graduates actually went into primary care in underserved areas. The key is to reward behavior, not intent. It is relatively easy for any medical center to designate a certain complement of residency positions as "primary care"; it is much more difficult to obscure the fact that the products of most medical schools end up practicing specialty medicine in affluent urban centers. Those who are successful in bucking the trend should be duly rewarded.

• *Eliminate glaring income disparities among physicians.* American physicians are well paid; with average net incomes well in excess of $100,000 annually, few physicians are starving.[74] The destructive aspect of our current physician income policy is the enormous gap between those at the high and the low ends of the scale. Struggling pediatricians in the urban community health center would probably feel a lot better about their wages if radiologists in the next building were not earning more than four times as much for less work and less responsibility.[75]

The current structure of physician reimbursement is a testament to chance, the power of narrow cartels, and the seduction of technology. The resource-based relative value scale is a modest step toward rationalizing the payment system, but we must be somewhat skeptical about the prospect that the new payment scheme will be translated into practice unscathed.[76] Despite these concerns, nothing sends a stronger signal about society's relative valuation of different specialties than the salaries it is willing to pay.

• *Adequately fund programs, such as the National Health Service Corps, that deploy and support physicians in underserved areas.* Even in the most exquisitely designed system of care, some segments of the population will lack adequate services. Whether or not we move in the direction of a nationalized health care system, it makes sense to have a program that allows the government to deploy physicians and other health care providers to areas of particular need.

The National Health Service Corps (NHSC) constitutes an existing program with the flexibility to address most of the areas or populations that experience real physician shortages. At its peak in 1986, the NHSC had a field strength of slightly more than 3,000 health professionals, most of whom were physicians providing obligated service in return for federal scholarships received during medical school. Since then, the number of NHSC personnel has declined precipitously, falling below 1,000 in 1990.[50] A reexpansion of the NHSC to its previously funded level would create a human resource pool that could be used to address the most severe shortages in the United States, as well as improve access to medical education for poor and minority students.[77] Doubling the NHSC staffing would virtually eliminate geographic maldistribution and would do much to mitigate the health problems of inner cities.

In conclusion, the debate about the relative surplus or shortage of physicians deflects attention from more fundamental issues of the selection and training of medical students and the structure of the larger health care system. Federal and state governments have shown that they can rapidly and dramatically affect the physician supply, and the doubling of the number of physicians in the past two decades is a direct result of deliberate governmental intervention. The government has been much less successful in affecting the composition of the physicians who are trained or in influencing what they do after graduation, largely because it has tacitly supported a schedule of economic awards to both teaching institutions and individual physicians that are much more powerful signals than unreinforced rhetoric.

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Conferences and Reviews

Pharmacology of Endothelium-derived Nitric Oxide and Nitrovasodilators

Moderator
LOUIS J. IGNARRO, PhD
Discussants
GORDON ROSS, MD, *and* JAN TILLISCH, MD

This is an edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

Nitric oxide is the active chemical species responsible for the vasodilator action of nitroglycerin, nitroprusside, and related nitrovasodilators. The most potent vasodilator and inhibitor of platelet aggregation known, nitric oxide was recently discovered to occur endogenously as the endothelium-derived relaxing factor. The pharmacology of endothelium-derived nitric oxide is virtually identical to that of the clinically used nitrovasodilators. Although endothelium-derived relaxing factor or endothelium-derived nitric oxide seems to be important in animals, its significance in humans still needs to be shown. We review the recent discoveries in the identification, biosynthesis, metabolism, and biologic actions of endothelium-derived nitric oxide, its significance in humans, and its relation to the clinically used nitrovasodilators.

(Ignarro LJ, Ross G, Tillisch J: Pharmacology of endothelium-derived nitric oxide and nitrovasodilators. West J Med 1991 Jan; 154:51-62)

Pharmacology of Nitric Oxide Vasodilators

LOUIS J. IGNARRO, PhD*: Nitroglycerin and sodium nitroprusside have been used clinically for many years as vasodilators. Both of these nitrogen oxide-containing vasodilators and other organic nitrate esters and organic nitrite esters (isoamyl nitrite) have been referred to as nitric oxide vasodilators or more simply as nitrovasodilators. The reason for this terminology is that after many years of not understanding their mechanism of action, studies have shown that such vasodilators produce their effects by generating nitric oxide in aqueous solution or in vascular smooth muscle. Nitric oxide itself can account for the vasodilator action of each of the nitrovasodilator drugs studied.

In the mid-1970s investigators found that nitroglycerin, sodium nitroprusside, and related vasodilators activated cytoplasmic guanylate cyclase and thereby stimulated cyclic guanosine 3′,5′-monophosphate (cyclic GMP) formation in vascular smooth muscle.[1-3] Nitric oxide was found to have similar biologic effects and was subsequently shown to be a potent, but transient, vascular smooth muscle relaxant when tested on isolated strips of bovine coronary artery.[4] It soon became clear that nitric oxide could account for the vascular smooth muscle relaxant properties of the nitrovasodilators.[5] Further studies suggested that chemical reactions between certain nitrovasodilators and free thiols, such as cysteine and glutathione, facilitated the decomposition of the parent drug accompanied by the generation of nitric oxide from intermediate unstable *S*-nitrosothiols.[5] In the closed chest of anesthetized cats, *S*-nitrosothiols were found to elicit hemodynamic responses that were indistinguishable from those elicited by nitroglycerin.[5] Based on earlier views expressed by Needleman and co-workers,[6,7] the proposal was forwarded that tolerance to nitroglycerin develops as a result of the depletion of smooth muscle free thiols so that *S*-nitrosothiols and therefore nitric oxide cannot be generated.[5] Tolerance to nitroglycerin in patients can be abolished, or partially reversed, by the intravenous infusion of *N*-acetylcysteine, which serves to restore the intracellular thiol concentration.[8-12]

At about the same time that the mechanism of action of the nitrovasodilators was being addressed, nitric oxide was discovered to activate platelet guanylate cyclase, elevate platelet cyclic-GMP levels, and inhibit human platelet aggregation.[13,14] It had been known previously that sodium nitroprusside inhibited platelet aggregation.

The physiologic significance of the findings that nitric oxide causes vascular smooth muscle relaxation and inhibition of platelet function remained elusive until recently, when nitric oxide was shown to occur naturally in mammalian vascular endothelial cells and to account for the vasodilator action of endothelium-derived relaxing factor (EDRF).[15-17] Endothelium-derived relaxing factor was first discovered in 1980 to account for the vascular smooth muscle relaxant action of acetylcholine[18] and was subsequently shown to activate cytoplasmic guanylate cyclase,[19] elevate vascular smooth muscle levels of cyclic GMP,[20] and inhibit platelet aggregation.[21]

The objective of this conference is to highlight the pharmacology and clinical significance of endothelium-derived nitric oxide and to review and compare the pharmacology and clinical effects of the nitrovasodilators.

*Professor of Pharmacology, UCLA School of Medicine.

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Reprint requests to Louis J. Ignarro, PhD, Department of Pharmacology, UCLA School of Medicine, Los Angeles, CA 90024-1735.

ABBREVIATIONS USED IN TEXT

cyclic AMP = cyclic adenosine 3′,5′-monophosphate
cyclic GMP = cyclic guanosine 3′,5′-monophosphate
EDRF = endothelium-derived relaxing factor
LDL = low-density lipoprotein

Biologic Actions of Nitric Oxide and Endothelium-derived Relaxing Factor

DR IGNARRO: The biologic actions of EDRF can best be described after considering the pharmacology and chemistry of nitric oxide and the nitrovasodilators. An appreciation of the biologic actions of nitric oxide will aid in the understanding of the potential physiologic and pathophysiologic significance of EDRF.

Pharmacology and Mechanism of Action of Nitric Oxide

Authentic nitric oxide is a highly unstable, gaseous free radical that is soluble in water to the extent of 1 to 3 mmol per liter and is biologically active at concentrations of 10 to 100 nmol per liter. Although nitric oxide is more stable as a concentrated solution in media of low oxygen tension, dilute biologically active solutions in oxygenated media have a half-life of only 3 to 5 seconds. Under such conditions, nitric oxide undergoes spontaneous inactivation by oxidation to nitrite (NO_2^-) and nitrate (NO_3^-). This oxidation reaction is catalyzed by oxygen-derived radicals such as superoxide anion and slowed by superoxide dismutase or low oxygen tension.

Activation of Soluble Guanylate Cyclase

Nitric oxide is a potent activator of the cytoplasmic enzyme guanylate cyclase, and this action accounts for the capacity of nitric oxide to stimulate cyclic-GMP accumulation in mammalian tissues.[2] Nitric oxide is one of the rare free radicals in biology that causes activation of an enzyme. The activation of guanylate cyclase by nitric oxide follows Michaelis-Menten kinetics, and the mechanism of enzyme activation is attributed to the interaction between nitric oxide and enzyme-bound heme.[22] Soluble guanylate cyclase is a hemoprotein and, as with other hemoproteins, the heme moiety has an extremely high binding affinity for nitric oxide and reacts with it to yield the nitric oxide-heme complex.[23] This nitric oxide-heme adduct represents the activated state of guanylate cyclase. Formation of the nitric oxide-heme complex at the porphyrin binding site results in a conformational change at or near the catalytic site, thereby increasing catalytic activity by as much as several hundredfold.[23] Kinetically, enzyme activation by nitric oxide is characterized by an increase in the maximal velocity and decreases in the Michaelis constant for both substrate and free uncomplexed metal cofactor.[24] Enzyme activation can be inhibited by oxidizing agents such as methylene blue or by other hemoproteins that compete for nitric oxide.[3] Thus, the activation of cytoplasmic guanylate cyclase by nitric oxide occurs by heme-dependent mechanisms. Purified enzyme from which heme is carefully removed, unlike heme-reconstituted enzyme, is unresponsive to nitric oxide.[25]

Vascular Smooth Muscle Relaxation

Nitric oxide elicits a potent and notable but transient relaxation of isolated preparations of artery and vein.[26] These relaxant responses are associated with guanylate cyclase activation and tissue cyclic-GMP accumulation, and vascular responses to nitric oxide are inhibited by methylene blue or hemoproteins. The hypothesis that cyclic GMP is a second messenger in mediating vascular smooth muscle relaxation in response to nitric oxide and nitrovasodilators[4,27] has received generally wide support during the past ten years. Cyclic adenosine 3′,5′-monophosphate (cyclic AMP), formed in vascular smooth muscle in response to prostacyclin, certain catecholamines, and other agents, also acts to mediate smooth muscle relaxation. Thus, both cyclic nucleotides can mediate a common biologic response in vascular smooth muscle. Arteries and veins respond similarly to nitric oxide, but venous smooth muscle seems to be more sensitive than arterial smooth muscle to the relaxant effect of nitric oxide and nitrovasodilators.[26]

Inhibition of Platelet Aggregation

Another important biologic action of nitric oxide is its capacity to inhibit as well as reverse platelet aggregation.[13] Nitric oxide and labile nitroso compounds that spontaneously liberate nitric oxide inhibit the aggregation of human platelets induced by adenosine diphosphate, collagen, thrombin, arachidonic acid, and thromboxanelike polyunsaturated fatty acids.[14] Nitric oxide can also reverse platelet aggregation in platelet-rich plasma. The mechanism by which nitric oxide inhibits platelet aggregation is virtually identical to its mechanism of vascular smooth muscle relaxation. Thus, nitric oxide activates platelet-soluble guanylate cyclase by heme-dependent mechanisms, rapidly and markedly elevates platelet cyclic-GMP levels, and inhibits platelet function. Whereas sodium nitroprusside is well known to inhibit platelet aggregation, nitroglycerin does not. The reason for this may be that nitroglycerin cannot be metabolized to nitric oxide within platelets as it can in vascular smooth muscle.

Prostacyclin also inhibits platelet aggregation[28] by the second messenger action of cyclic AMP.[29] Thus, once again cyclic GMP and cyclic AMP play similar roles in modulating cell function. Indeed, synergistic effects on the inhibition of platelet aggregation can be elicited by combining substances that elevate cyclic-GMP and cyclic-AMP levels.[30]

Cytotoxic Action in Macrophages

Mammalian macrophages in the activated state can synthesize relatively large quantities of inorganic nitrite and nitrate in the absence of any anaerobic microorganisms. Cytotoxic-activated murine macrophages synthesize nitrite and nitrate in response to certain lipopolysaccharides, lymphokines, and related factors.[31] This synthesis can be enhanced in the presence of T lymphocytes. Both nitrite and nitrate seem to be synthesized from L-arginine, as the nitrogen atom can be derived exclusively from the terminal guanidino nitrogens of L-arginine.[32] Nitrite and nitrate have been implicated in the cytotoxic action of activated macrophages because L-arginine is needed for the expression of the activated macrophage effector mechanism causing selective cytotoxicity.[33] New insights provide evidence that nitric oxide is an intermediate in the conversion of L-arginine to nitrite and nitrate in cytotoxic-activated macrophages and that the nitric oxide itself seems to be responsible for mediating the cytotoxic action of these cells.[34]

This important discovery may have implications in vascular and platelet function as well. The nitric oxide generated

by activated tissue macrophages may diffuse to nearby capillaries where it elicits local vasodilator responses and inhibits local platelet aggregation. Such local actions of nitric oxide could facilitate the cytotoxic function of tissue macrophages by improving local blood flow and preventing local thrombosis at the site of macrophage-infiltrated tissue.

Mechanism of Action of Nitroglycerin

Nitroglycerin, or glyceryl trinitrate, is one of several available organic nitrate esters used clinically as vasodilators to treat patients with angina, congestive heart failure, and other cardiovascular disorders. Nitroglycerin has been used in this capacity for more than a century, although its mechanism of action remained a complete mystery until the 1970s. Other organic nitrate esters that possess a similar mechanism of action include isosorbide dinitrate, pentaerythritol tetranitrate, and erythrityl tetranitrate. Organic nitrite esters (isoamyl nitrite) and sodium nitroprusside, although chemically distinct from nitroglycerin, have a similar mechanism of action.

Release of Nitric Oxide

Inorganic nitrite (NO_2^-) reacts in aqueous acid to yield nitrous acid and nitric oxide, but this reaction is slow at biologic pH, and nitrite is therefore only a weak vasodilator. In the presence of free thiols or sulfhydryl groups, however, nitrite rapidly generates nitric oxide by forming the labile intermediate *S*-nitrosothiol.[5,35] For example, nitrite reacts with cysteine to yield *S*-nitrosocysteine, which, in turn, spontaneously decomposes to generate free nitric oxide plus cystine (the disulfide of cysteine). *S*-Nitrosothiols are potent vasodilators that mimic the cardiovascular hemodynamic actions of nitroglycerin.[5] Although nitric oxide activates soluble guanylate cyclase in the absence of added thiols, enzyme activation by nitroglycerin and other organic nitrate esters cannot occur appreciably in the absence of added cysteine.[5,35] The active species is nitric oxide that is generated spontaneously from the labile *S*-nitrosocysteine formed in the reaction. Enzyme activation by *S*-nitrosocysteine is indistinguishable in mechanism from that caused by nitric oxide. These findings are compatible with earlier studies showing the requirement of tissue thiols for arterial relaxation elicited by organic nitrate esters and suggesting that nitroglycerin interacts with sulfhydryl-containing receptors.[6,7] The mechanism of action for nitroglycerin is shown schematically in Figure 1.

Tolerance

The repeated or long-term administration of high doses of nitroglycerin can lead to the development of tolerance or refractoriness to the vascular smooth muscle relaxant effect of nitroglycerin and other organic nitrate esters with little or no cross-tolerance to sodium nitroprusside. The first clue to the mechanism of the development of tolerance to nitroglycerin came from studies that also provided the first clue to its mechanism of vascular smooth muscle relaxation.[6,7] Tissue sulfhydryl groups were found to be needed for arterial relaxation elicited by organic nitrate esters, sodium nitroprusside, inorganic nitrite, and related vasodilators. The relaxant effects of all agents were blocked by nonselective thiol alkylating agents. On repeated testing, refractoriness to vascular smooth muscle relaxation developed only to the organic nitrate esters. The development of tolerance to nitroglycerin was associated with a concomitant decrease in detectable free sulfhydryl groups as well as the formation of nitrite from nitroglycerin in the tissues. Normal tissue responsiveness was restored by adding thiol reducing agents. The conclusion reached was that nitroglycerin interacts selectively with a population of tissue sulfhydryl groups that is distinct from those sulfhydryl groups that interact with nitroprusside or nitrite. A plausible hypothesis was that nitroglycerin oxidizes selective sulfhydryl-containing receptors to the disulfide form and that the latter displays only a low binding affinity for nitroglycerin. More recent studies were confirmatory and showed that the development of tolerance to vascular smooth muscle relaxation elicited by nitroglycerin is accompanied by a concomitant development of tolerance to the cyclic-GMP-accumulating action of nitroglycerin.[36-38] Vascular tolerance to nitroglycerin was not associated with appreciable cross-tolerance to nitroprusside or cyclic GMP.

These findings are consistent with more recent proposals that organic nitrate esters need interaction with cysteine to generate *S*-nitrosocysteine and nitric oxide to cause vascular smooth muscle relaxation.[5] Arterial and venous smooth muscle preparations rendered tolerant to the actions of nitroglyc-

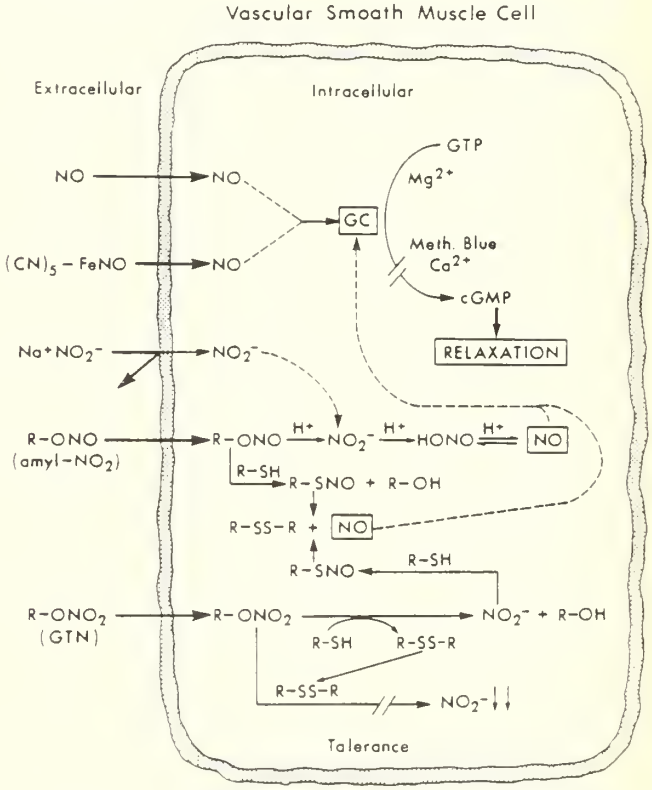

Figure 1.—The schematic illustration shows the proposed mechanism of vascular smooth muscle relaxation elicited by nitrovasodilators. Nitric oxide (NO) is lipophilic, readily permeates the plasma membrane, activates cytoplasmic guanylate cyclase (GC), and elevates intracellular levels of cyclic guanosine 3',5'-monophosphate (cGMP). Inorganic nitrite (NO_2^-) is charged, and only limited amounts can permeate the cell, but intracellular nitrite can be converted to NO. Lipophilic organic nitrite, or nitrate esters (R-OH), readily permeate cells and can be converted to nitrite and NO in chemical reactions that are facilitated by thiols (R-SH) and acidic conditions. *S*-Nitrosothiols (R-SNO) are labile intermediates that decompose spontaneously with the generation of NO. Organic nitrate esters ($R-ONO_2$) specifically need one pool of thiols, such as cysteine, to generate NO, and intracellular thiol deficiency results in the development of selective tolerance or refractoriness to their pharmacologic actions. Adapted from Ignarro et al.[5] $(CN)_5$-FeNO = nitroprusside, GTN = glyceryl trinitrate or nitroglycerin, GTP = guanosine triphosphate, HONO = nitrous acid, Meth. Blue = methylene blue, R-ONO = organic nitrite ester, R-SS-R = disulfide

erin are still fully responsive to *S*-nitrosothiols and nitric oxide. Clinical studies have supported the above interpretations by showing that intravenous infusions of *N*-acetylcysteine improved the responsiveness of tolerant patients to nitroglycerin for the treatment of angina or improved coronary sinus blood flow.[8,9,11,12] The results of additional studies have supported this view.[10,39-43]

Other Nitrovasodilators

The organic nitrite esters, such as isoamyl nitrite, elicit vascular smooth muscle relaxation by a mechanism that is similar to that of nitroglycerin and the other organic nitrate esters. The principal difference is that the organic nitrite esters can react not only with cysteine but also with various thiols to yield the corresponding *S*-nitrosothiols.[5,35] Thus, the mechanism of action of organic nitrite esters is essentially the same as that of any nitrovasodilator, that is, vasodilators that liberate nitric oxide. Sodium nitroprusside is an inorganic nitroso compound (nitrosoferricyanide) that is unstable in aqueous solution and liberates nitric oxide in the absence of added thiols. Tolerance or refractoriness does not generally develop to organic nitrite esters or nitroprusside because, unlike nitroglycerin, these nitrovasodilators do not interact selectively with only one population of tissue sulfhydryl groups.

Pharmacology of Endothelium-derived Relaxing Factor

Endothelium-derived relaxing factor is released from endothelial cells lining the intimal surface of both artery and vein and from freshly harvested or cultured vascular endothelial cells. Numerous chemically diverse substances, including amines, peptides, fatty acids, and adenine nucleotides, interact with selective receptors on the endothelial cell surface that are coupled to intracellular processes associated with the generation of EDRF. Bioassay techniques have proved to be instrumental in evaluating the pharmacologic and chemical properties of EDRF. Such studies led to the characterization and identification of EDRF as nitric oxide or a labile nitroso compound that spontaneously liberates nitric oxide.

Actions on Vascular Smooth Muscle

Oxygen, calcium, and adenosine triphosphate-derived energy sources are required for, whereas magnesium attenuates, endothelium-dependent arterial relaxation. Endothelium-dependent relaxation is antagonized by hemoglobin, related hemoproteins, methylene blue, high oxygen tension, and superoxide anion.[44] Hemoglobin binds EDRF, methylene blue inhibits soluble guanylate cyclase activation, and oxygen or oxygen-derived radicals catalyze the oxidative inactivation of this relaxing factor. Endothelium-dependent relaxation can be partially antagonized by chemical agents that interfere with phospholipid or arachidonic acid metabolism, including quinacrine hydrochloride, nordihydroguaiaretic acid, eicosatetraenoic acid, proadifen hydrochloride (US Pharmacopeial Convention code designation SK&F-525A), metyrapone, and gossypol,[45] although the relation between this effect and EDRF generation is unknown. The chemical and pharmacologic properties of EDRF released from perfused artery, vein, freshly harvested endothelial cells, or cultured endothelial cells seem to be indistinguishable as assessed by bioassay cascade in the presence of indomethacin and by the activation of soluble guanylate cyclase.[44] Thus, one common EDRF may be responsible for vascular smooth muscle relaxation. Table 1 lists the salient chemical and pharmacologic properties of arterial and venous EDRF.

TABLE 1.—*Pharmacologic and Chemical Properties of Arterial and Venous Endothelium-derived Relaxing Factor*

Cause endothelium-independent relaxation of vascular smooth muscle
Cause relaxation of nonvascular smooth muscle
Inhibit platelet aggregation and adhesion to endothelium
Activate soluble guanylate cyclase by heme-dependent mechanisms
Elevate cyclic guanosine 3′,5′-monophosphate levels in vascular and nonvascular smooth muscle and in platelets
Biologic actions are terminated by methylene blue, hemoglobin, and myoglobin
Lipophilic; readily permeate biologic membranes
Chemically unstable in presence of oxygen (half-life 3 to 5 s); accelerated by superoxide anion
Biologic actions are enhanced by superoxide dismutase or low oxygen tension
React with sulfanilic acid (diazotization reaction)
React with deoxyhemoglobin to yield nitric oxide-hemoglobin
React with oxyhemoglobin to yield methemoglobin
React with ozone in a chemiluminescence reaction

Actions on Platelets

In 1981 we found that nitric oxide caused a potent and pronounced inhibition of human platelet aggregation associated with greatly elevated platelet cyclic-GMP levels and that such responses were antagonized by hemoglobin.[13] Five years later EDRF released from perfused rabbit aorta was shown to inhibit platelet aggregation.[21] Endothelium-intact arterial rings, or cultured umbilical vein endothelial cells, inhibited platelet aggregation by mechanisms that were antagonized by hemoglobin, methylene blue, and gossypol and enhanced by superoxide dismutase.[46,47] Endothelium-derived relaxing factor generated from cultured aortic endothelial cells inhibited platelet aggregation in an identical manner as that found by authentic nitric oxide.[48] The antiaggregatory actions of EDRF and nitric oxide, but not prostacyclin, were potentiated by zaprinast (code designation M&B 22948; an inhibitor of cyclic-GMP phosphodiesterase) and superoxide dismutase and were inhibited by hemoglobin and ferrous ion. Prostacyclin and EDRF are distinct endothelium-derived substances that cause vasodilation and inhibit platelet aggregation. Endothelium-derived relaxing factor but not prostacyclin, however, inhibits the adhesion of platelets to the vascular endothelial surface[49]; these two agents together produce synergistic antiaggregatory effects on platelets.[30]

Identification as Nitric Oxide

The pharmacologic and chemical properties listed in Table 1 for EDRF are virtually indistinguishable from the properties of authentic nitric oxide.[50] The chemical identification of EDRF as nitric oxide was achieved by three different methods: reactivity with ozone to cause photon emission (chemiluminescence) from an activated nitrite species[15]; reactivity with deoxyhemoglobin to generate nitric oxide-hemoglobin[17]; and diazotization of sulfanilic acid.[16] This chemical characterization has been done not only for freshly harvested or cultured vascular endothelial cells but also for endothelium-intact artery and vein. These findings indicate clearly that nitric oxide accounts for many, if not all, of the biologic properties of the endothelium-dependent relaxants

first described by Furchgott and Zawadzki.[18] The possibility still remains, however, that endothelium-derived nitric oxide is a labile nitroso compound rather than free nitric oxide, as the chemical and biochemical assays used cannot distinguish between the two. But it is highly likely that, operationally, the important part of any nitroso compound would be nitric oxide itself.

Biosynthesis and Termination of Action

Studies with cytotoxic-activated macrophages showing that nitrite and nitrate can be synthesized from L-arginine[32] led to the findings that mammalian aortic endothelial cells can synthesize nitric oxide and nitrite from L-arginine.[51] Both the formation of nitric oxide from L-arginine and endothelium-dependent relaxation are antagonized by close structural analogues of L-arginine, such as L-*N*-monomethyl arginine and L-canavanine.[51-54] The most recent study to date suggests that a reduced nicotinamide adenine dinucleotide phosphate-requiring monooxygenase is involved in the conversion of L-arginine to nitric oxide.[55] Whether arginine-containing peptides or other basic amino acids or peptides can also serve as precursors to nitric oxide is unknown. Moreover, the process by which the interaction between endothelial cell receptors and endothelium-dependent relaxants is coupled to the enzymatic conversion of L-arginine to nitric oxide is unknown.

The major mechanism for the termination of the biologic action of endothelium-derived nitric oxide seems to be a rapid spontaneous oxidative conversion to nitrite, which is only a weak vascular smooth muscle relaxant. Because of the short half-life (3 to 5 seconds) of nitric oxide in oxygen-containing aqueous medium, it is unlikely that enzymatic, or reuptake, mechanisms play any role in terminating the action of endothelium-derived nitric oxide. Other mechanisms may be involved, including the presence of any superoxide anion that may be generated concomitantly with endothelium-derived nitric oxide as well as the presence of hemoglobin or myoglobin. Superoxide anion catalyzes the oxidation of nitric oxide, whereas hemoproteins bind and thereby inactivate nitric oxide. These actions likely participate in preventing more widespread or downstream actions of endothelium-derived nitric oxide.

Clinical Significance

Any fundamental knowledge of the biologic actions and mechanisms of action of EDRF could prove to be of clinical importance. The uncovering of a new mechanism of endogenously mediated local vasodilation and the inhibition of thrombosis has stimulated new concepts about the possibility of such a mechanism representing a form of autoregulation of local blood flow. For example, flow-induced vasodilation may be mediated by EDRF generated in response to increased shear force at the endothelium. The possibility that local tissue hormones, such as bradykinin and histamine, elicit their vasodilator actions through EDRF shows how such actions could be modulated or artificially controlled in pathologic states. Although many questions need to be answered, it is tempting to entertain the idea that vascular endothelial cell injury could cause a decrease in the local generation of EDRF and that such a state could trigger local vasospasm or platelet aggregation, or both. This would be more significant if the normal healthy vascular endothelium continuously generates even small quantities of EDRF to maintain vessel patency and prevent platelet adhesion to the endothelial surface. Moreover, one could envision how locally generated superoxide anion, or other oxygen-derived radicals, could accelerate the inactivation of EDRF and thereby provoke a similar pathophysiologic response. The presence of free hemoglobin in or around a capillary network occurring as a result of local tissue injury could conceivably bind and inactivate EDRF. Such an occurrence in the brain could provoke local vasoconstriction with potentially deleterious consequences.

Relation to Nitrovasodilator Drugs

The most important relation between EDRF and nitrovasodilator drugs is their common mechanism of action. Nitric oxide is the common chemical agent responsible for the vascular smooth muscle relaxant action of EDRF and the nitrovasodilator drugs. Experimentally and clinically, however, notable differences in responses are often seen among authentic nitric oxide, labile nitroso compounds, sodium nitroprusside, and organic nitrate esters like nitroglycerin. Hemodynamic differences may be found after intravenous administration. Differences in potency or magnitude of responses may be seen using in vitro preparations. The reasons for such differences are likely to be pharmacokinetic in nature—that is, nitric oxide itself is extremely unstable, whereas sodium nitroprusside is more stable. Sodium nitroprusside spontaneously generates nitric oxide, whereas nitroglycerin must be metabolized in the vascular smooth muscle to liberate nitric oxide. Moreover, nitroglycerin is rapidly metabolized and inactivated in the liver. The failure of nitroglycerin to inhibit platelet aggregation, whereas nitric oxide and sodium nitroprusside markedly inhibit platelet aggregation, can be attributed to a failure of the platelets to metabolize nitroglycerin to nitric oxide. With the current knowledge that EDRF is nitric oxide or a labile nitroso compound, there is no doubt that new nitrovasodilator drugs will become available that differ in the availability of the nitroso or nitric oxide function. For example, *S*-nitrosothiols can be developed that are not metabolized in the liver but are unstable in aqueous solution or in body fluids. Nitroso compounds that differ in the rate of liberation of nitric oxide in solution may be of value. Nitroso compounds could be developed for use as antithrombotic agents because the liberated nitric oxide would inhibit platelet aggregation and adhesion to the vascular endothelial surface.

Endothelium-derived Relaxing Factor and Atherosclerosis

GORDON ROSS, MD*: Although nitrovasodilators have been used in the treatment of angina for more than 120 years, their mechanism of action is still not completely characterized. The British physician T. Lauder Brunton,[56] who used amyl nitrite in 1867 to relieve severe nocturnal chest pain in a patient, thought that its action was related to a reduction in arterial pressure. Subsequently, the potent venodilator effect of nitrates with a reduction in ventricular preload, wall tension, and myocardial oxygen demand was considered to be the dominant therapeutic mechanism. In 1869 Huchard[57] speculated that nitrates dilated coronary arteries, but another 60 to 70 years passed before angiography showed that coronary artery diameter could change spontaneously in response to drugs, including nitroglycerin.

*Professor of Medicine, Division of Cardiology, UCLA School of Medicine.

Detailed studies of coronary artery reactivity in patients are difficult not only because of the discomfort and possible risk to patients but because of many confounding variables. Therefore, we began in 1976 to study the responses of isolated human coronary arteries in tissue baths. Initially the arteries were obtained from autopsies four to eight hours after death. They were cut into ring segments 2 to 5 mm long and mounted on force transducers that measured isometric tension. Surprisingly, the arteries developed remarkable spontaneous rhythmic contractions, a behavior quite different from animal coronary arteries, which are quiescent under these conditions. Similar rhythmicity was shown by arteries freshly obtained from heart transplant recipients.[58] Various manipulations, including rinsing, passive stretch, and the addition of constrictor agents, including norepinephrine, histamine, acetylcholine, prostaglandin $F_{2\alpha}$, and ergonovine, also induced rhythmic responses when added during a quiescent period. The responses were often similar to each other and to the spontaneous contractions (Figure 2). It was as if the vessel were programmed to respond in a certain way no matter what the trigger.

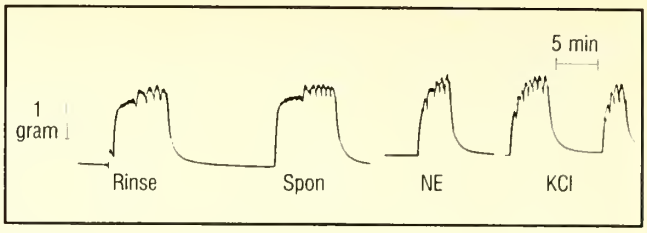

Figure 2.—Phasic contractions of an isolated coronary artery ring segment are shown. Contractions induced by rinsing with regular Krebs solution **(Rinse)** or by adding norepinephrine **(NE)**, 10^{-6} mol per liter, or potassium chloride **(KCl)**, 20 mmol per liter, resemble those occurring spontaneously **(Spon)**.

Responses of Isolated Human Coronary Arteries to Nitroglycerin

When phasic contractions occur spontaneously, or are induced by agonists, nitroglycerin reduces the level of tone from which the contractions spring; it has less effect on the amplitude of contractions, however, even when high concentrations are used (Figure 3, top tracing). Digitalis glycosides, such as ouabain, convert phasic contractions to a sustained tonic response, which is relatively resistant to nitroglycerin (Figure 3, middle tracing). This resistance is not attributable to an inhibition of the sodium pump alone because high concentrations of ouabain, in the absence of other agonists, cause contractions that are readily inhibited by low doses of nitroglycerin (Figure 3, bottom tracing). It is likely that the conversion of an agonist response from phasic to tonic and the diminished effect of nitroglycerin in the presence of ouabain are associated with the greater depolarization produced by the agonist-ouabain combination. In rabbit coronary arteries, ouabain alone reduced the membrane potential of the smooth muscle cells from −55 to −39 mV and the combination of 2-(2-aminoethyl)-pyridine and ouabain from −55 to −28 mV.[59] Unfortunately, it has not been possible to study human coronary arteries electrophysiologically. Increasing the bath concentration of potassium [K]o, however, causes a significant reduction in the relaxation responses to nitroglycerin (Figure 4). This is indirect evidence that membrane depolarization, or an associated phenomenon, inhibits nitroglycerin effects.

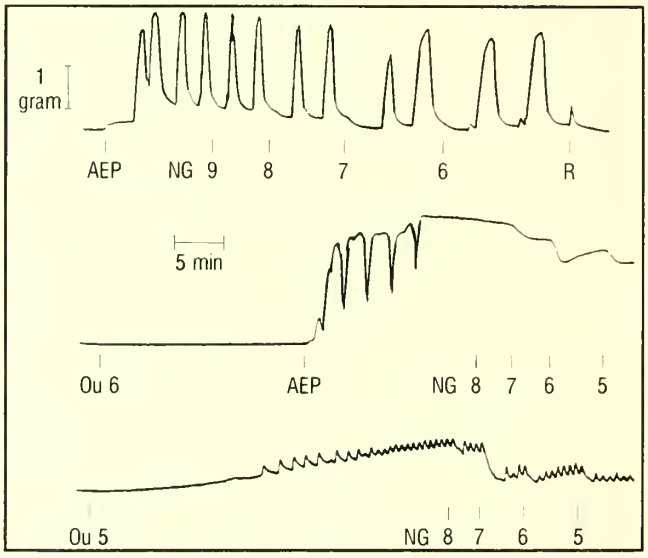

Figure 3.—**Top trace,** The effects of nitroglycerin **(NG)** are shown on phasic responses induced in an isolated human coronary artery ring by 2-(2-aminoethyl)-pyridine **(AEP)**, a histamine H-1 receptor agonist. Numbers are negative logarithms of molar concentrations. Note that large phasic contractions still occur despite high NG concentrations. **Middle trace,** After pretreatment with ouabain **(Ou)** 10^{-6} mol per liter, AEP produces phasic contractions that become tonic; nitroglycerin is relatively ineffective in relaxing this tonic response. **Bottom trace,** A higher concentration of ouabain (10^{-5} mol per liter) produces a contraction in the absence of other agonists. This contraction is relaxed almost to baseline by nitroglycerin.

As in other vessels, there is evidence that nitroglycerin-induced dilation of human coronary arteries is mediated by soluble guanylate cyclase and cyclic-GMP accumulation. Bossaller and colleagues showed that cyclic-GMP levels of human coronary artery strips increased fivefold after 60 seconds of exposure to 1 μmol per liter of nitroglycerin.[60]

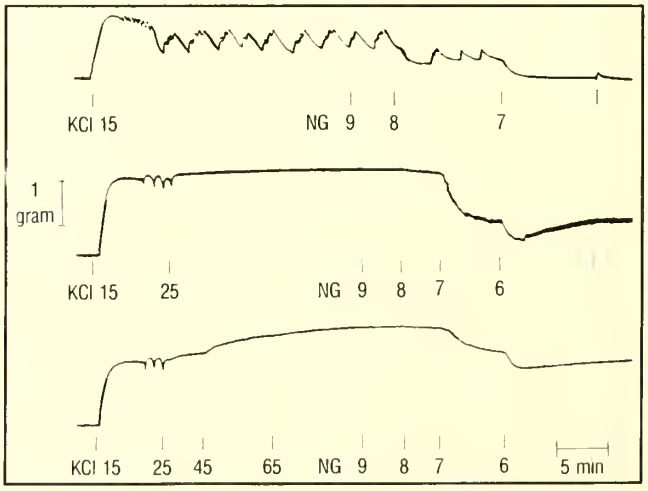

Figure 4.—The effects of increasing concentrations of nitroglycerin **(NG)** on potassium chloride **(KCl)**-induced contractions are shown in an isolated human coronary artery ring. **Top trace,** The KCl concentration is 15 mmol per liter. **Middle trace,** The KCl concentration is increased to 25 mmol per liter. **Bottom trace,** The KCl concentration is increased progressively to 65 mmol per liter. The numbers after NG are negative logarithms of molar concentrations.

Endothelium-derived Relaxing Factor and Human Coronary Arteries

Effects of Atherosclerosis

In vitro studies. Förstermann and associates studied coronary arteries precontracted with prostaglandin $F_{2\alpha}$ from two groups of heart transplant recipients.[61] One group comprised

six young patients (aged 14 to 25) with cardiomyopathy. Their arteries were free of atherosclerotic plaques and showed pronounced endothelial-dependent relaxation to substance P, calcium ionophore, and bradykinin. The other group comprised 11 older patients (42 to 55) with notably atherosclerotic arteries. The proportion of intimal surface covered by intact endothelium was similar in both groups. The relaxation responses of these atherosclerotic vessels to these agents were substantially less. Acetylcholine rarely caused relaxation in either group. Isoproterenol, which uses cyclic AMP as its second messenger, relaxed both groups equally. Responses to low doses of nitroglycerin were attenuated in the atherosclerotic arteries, but responses to high doses were similar in both groups.

Bossaller and colleagues also compared atherosclerotic and normal coronary arteries from transplant recipients.[60] Responses to substance P were diminished in the atherosclerotic vessels, but calcium ionophore gave similar relaxations in both groups. Acetylcholine relaxed nonsclerotic vessels but failed to relax sclerotic arteries. The reason for the discrepancies between these two similarly conducted studies is unclear.

Berkenboom and co-workers found that substance P relaxed coronary arteries with no or minimal atherosclerosis.[62] The relaxation was substantially reduced by moderate atherosclerosis and was abolished by advanced atherosclerosis.

In our laboratory we tested responses to acetylcholine in 23 patients, including 8, aged 8 to 20, who received heart transplants for cardiomyopathy. Acetylcholine contracted all vessels, and relaxation never occurred. Substantial endothelial-dependent relaxations were evoked by substance P (10^{-10} to 10^{-7} mol per liter) and calcium ionophore 10^{-7} to 10^{-6} mol per liter (Figure 5). Bradykinin (10^{-8} to 10^{-6} mol per liter) induced relaxation in four of eight vessels; the remaining four vessels showed no response, although they did respond to substance P, and intact endothelium was shown by silver staining. Thus, in vitro studies have shown that human coronary arteries present endothelium-dependent relaxation but differ from animal arteries in rarely showing relaxation to acetylcholine. Although the number studied is small, several studies suggest that coronary artery disease impairs endothelial-dependent relaxation. Whether this is due to impaired release or to diminished response to EDRF is uncertain; there is conflicting evidence of whether atherosclerosis produces a selective or a nonselective impairment of EDRF release.

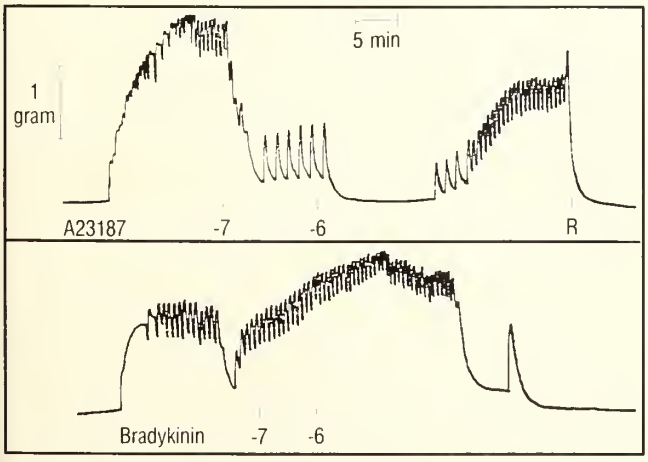

Figure 5.—The effects of a calcium ionophore, A23187, and bradykinin are shown on contractions induced by 2-(2-aminoethyl)-pyridine in an isolated human coronary artery ring. **Upper trace,** A23187 induced relaxation, whereas **(lower trace)** bradykinin caused further contraction. The numbers are negative logarithms of molar concentrations.

In vivo studies. The few in vivo studies have used acetylcholine, which is not an ideal agent because it can produce vasoconstriction that could mask vasodilator responses. Ludmer and associates infused acetylcholine into the anterior descending coronary arteries of 18 patients and measured diameter changes by quantitative angiography.[63] In four women with atypical chest pain, acetylcholine increased the diameter of normal coronary arteries by a mean of 11%. In six patients with minimal disease (<20% stenosis), acetylcholine constricted both the diseased segments and adjacent smooth segments. In eight patients with more severe disease (>50% stenosis), the infusion caused temporary occlusion in five.

Nellessen and colleagues infused acetylcholine into the left coronary arteries of ten patients who had undergone heart transplantation one to eight years previously.[64] All had angiographically normal vessels and negative exercise tests. No coronary artery dilation was found, and all the infused arteries constricted. In another four patients, who had not undergone a previous operation, acetylcholine was infused into vessels preconstricted with phenylephrine. Further constriction developed in all cases. Horio and co-workers injected acetylcholine into the coronary circulation of 30 patients.[65] Constriction was the usual response, but dilation did occur in some patients. Considerable variation in response occurred in different parts of the arterial tree. Hodgson and Marshall administered bolus injections of acetylcholine into normal, or near-normal, coronary arteries of patients undergoing angiography[66]; only constriction occurred. On the other hand, Werns and associates found that intracoronary acetylcholine caused a 6% increase in the diameter of smooth coronary arteries in patients without coronary artery disease but a 9% decrease in the diameter of angiographically normal coronary arteries of patients with coronary artery disease.[67]

Thus, in vivo studies so far have shown inconsistent responses to acetylcholine. There is no unequivocal evidence for the release of EDRF from the intact human coronary artery circulation, but acetylcholine-induced constriction is clearly greater in atherosclerotic vessels than in normal ones.

In Vitro Studies in Animals

Effects of Atherosclerosis

The possibility that atherosclerosis may be associated with diminished EDRF release has prompted many investigators to assess its role in influencing arterial reactivity in animal models. Freiman and co-workers compared acetylcholine responses in two groups of monkeys.[68] One group was fed a normal diet and the other was fed a high-fat, high-cholesterol diet for 18 months. Endothelium-dependent relaxation of iliac arteries to acetylcholine and thrombin was significantly reduced in the atherosclerotic vessels. The responses of veins were similar in the two groups, suggesting that hypercholesterolemia was not solely responsible for the differences seen in the arterial responses.

Jayakody and colleagues compared the responses of aortas from normal and atherosclerotic rabbits who had been fed a diet that increased the plasma cholesterol level to 51.72 mmol per liter (2,000 mg per dl).[69] After four weeks, endothelium-dependent relaxation of ring segments precontracted

with norepinephrine was significantly reduced in the rabbits with high cholesterol levels, but the responses to sodium nitrite, an endothelium-independent vasodilator, were similar. In five animals fed a high-cholesterol diet for six weeks and then a normal diet for 32 weeks, serum cholesterol levels returned to normal but the aortas remained atherosclerotic and acetylcholine-induced relaxation remained impaired. Thus, the endothelial defect is not readily reversed in this model.

Jayakody and colleagues subsequently showed that age was an important factor in determining the effects of high-cholesterol diets.[70] Young 8-week-old animals fed a high-cholesterol diet for four weeks increased their plasma cholesterol levels to 49.13 mmol per liter (1,900 mg per dl), and striking subintimal lesions developed. On the other hand, atherosclerotic lesions did not develop in older rabbits 46 weeks of age, and serum cholesterol levels rose to only 14.74 mmol per liter (570 mg per dl). Both groups had similar impairment of acetylcholine-induced relaxation, and both had endothelial cell lesions. This suggests that atherosclerosis per se is not the cause of the endothelial defect.

Cohen and associates fed seven pigs a high-fat, high-cholesterol diet for nine weeks.[71] Plasma cholesterol levels rose to 15.52 mmol per liter (600 mg per dl), but no atherosclerotic changes were seen by light microscopy and only minimal endothelial changes were seen by electron microscopy. Isolated coronary arteries precontracted with norepinephrine from hypercholesterolemic animals showed an impaired endothelial-dependent dilator response to substance P but unimpaired responses to calcium ionophore. Thus, in this species of hypercholesterolemic animals a selective endothelial cell dysfunction seemed to develop, leading to abnormal coronary artery reactivity before atherosclerosis developed.

Andrews and co-workers showed that rabbit aortic rings exposed to 1 to 2 mg per ml of human low-density lipoproteins (LDLs) showed reduced relaxation to acetylcholine, adenosine triphosphate, and calcium ionophore.[72] Incubation with LDLs for at least 10 minutes was needed; maximum effects were seen in 20 to 30 minutes and persisted even after 2 hours of rinsing with LDL-free solution. Responses to sodium nitroprusside were not inhibited. When LDLs were modified with cyclohexanedione, the inhibitory effect was reduced by 65%. This suggests that the inhibition of endothelium-dependent relaxation by LDLs was mediated by the LDL receptor and not through a nonspecific mechanism.

Evidence from studies of animals and humans thus indicates that atherosclerosis modifies arterial responses to vasoactive drugs through mechanisms that result in impaired production or release of endothelium-derived relaxing factor. In some animal models, this impairment may be related to hyperlipidemia and may precede macroscopic changes in the arterial wall. It remains to be determined whether abnormal lipid levels in patients are associated with altered EDRF function.

Clinical Use of Nitrates

JAN TILLISCH, MD*: The use of nitroglycerin for the treatment of angina is well established. In recent years, nitroglycerin and nitroprusside have been shown to be effective in the initial treatment of congestive heart failure,[73,74] and various forms of nitrates have been effective in the long-term treatment of heart failure.[75,76] The expanding use of nitrates in the treatment of acute and chronic manifestations of ischemic heart disease and congestive heart failure is mainly due to a better understanding of the pathophysiologic targets of these agents.

Nitrates in Ischemic Heart Disease

The imbalance between myocardial oxygen supply and demand results in the symptomatic expression of angina and eventually in the myocardial ischemic injury. Oxygen supply, limited in atherosclerotic coronary disease by the obstructive lesion, is a function of the residual lumen cross-sectional area, length of the stenosis, perfusion pressure, and available collateral support. It is affected to a lesser degree by heart rate and duration of systole, which determine the diastolic coronary artery perfusion time and by the left ventricular diastolic pressure, which affects the coronary artery perfusion gradient for the left ventricle. Myocardial oxygen demand is a function of heart rate, ventricular volume through its effect on wall tension, impedance to ejection (arterial resistance and compliance), and the contractile state of the myocardium.

The traditional view of ischemic heart disease is that the oxygen supply is largely fixed by the obstructive lesion and that angina results from periodic excessive demand relative to that supply. As the lesion progresses in severity, complete occlusion may occur or, alternatively, abrupt changes in the lesion caused by hemorrhage into the plaque, or fissuring with exposure of a thrombogenic surface, may suddenly result in progression from subclinical to occlusive coronary artery disease. The therapeutic targets in this traditional view are primarily the oxygen demand determinants. Nitrates, through a reduction in venous return and arterial resistance, reduce wall tension and thus necessary oxygen consumption.[77] Any effects on oxygen supply have in the past been due to improved collateral flow through dilation of the nonobstructed coronary arteries and perhaps collateral channels.[78]

Several studies during the past decade have expanded our concepts of the pathophysiology of ischemic heart disease. First, it is now recognized that angina is just the tip of the ischemic iceberg. Silent ischemia may occur much more frequently with nonexertional instigating factors.[79] In addition, chronically underperfused myocardium may "autoregulate" its contraction to meet its supply, resulting in viable noncontracting myocardium.[80] Efforts to reduce oxygen demand will have little influence on the function of "hibernating" myocardium, nor will they substantially reduce the frequency of silent ischemic episodes, which are not precipitated by increased blood pressure, pulse rate, or other factors that raise oxygen demand.[81]

Studies by Brown and associates and Maseri and coworkers have shown that the arterial luminal area at the atherosclerotic lesion is not fixed but is potentially dynamic in most lesions.[82,83] In addition, it is now recognized that coronary arteries do vasoconstrict even in ischemia. α-Sympathetic agonists, platelet-generated thromboxane, serotonin, and other mediators may cause a small but critical decrease in luminal area with major effects on coronary artery flow. As described previously, the loss of intrinsic endothelium-produced "relaxing factor"—nitric oxide—at the region of atherosclerotic disruption of the normal vascular architecture may lead to vasoconstrictive responses to stimuli that might otherwise be vasodilatory. Brown and colleagues have also

*Associate Professor of Medicine, Division of Cardiology, UCLA School of Medicine.

shown that isometric exercise may induce ischemia by presumed neurally mediated vasoconstriction at the eccentric atherosclerotic lesion, leading to ischemia by decreasing supply rather than increasing demand.[84] It is clear from these and other studies that the region of the atherosclerotic lesion is itself a major potential target. Nitroglycerin and other nitrovasodilators have shown effects on that target.[85,86]

Additional benefits of nitrates include an increase in collateral flow associated with conductance arterial dilation and also the demand-reducing effects of peripheral arterial vasodilation and venodilation. These latter effects on oxygen demand may have particular benefit on the "nonischemic" zone supporting the contractile burden during periods of decreased contraction in the ischemic region.

Nitroglycerin has its dominant dilating effect on the medium-sized conductance artery, whereas nitroprusside has a greater effect on resistance arterioles; nitroglycerin is therefore more suitable for use in patients with ischemia. We examined the comparative effects of nitroglycerin and nitroprusside on regional wall motion at comparable left ventricular filling pressures in patients with depressed left ventricular function within 24 hours of an acute myocardial infarction. The two agents were similar in effect on systemic vascular resistance and cardiac index (Table 2), but the administration of nitroglycerin resulted in a higher stroke work index and improved regional ejection fraction in the infarct zone, whereas nitroprusside had a greater effect on the noninfarct zone. Other studies have clearly shown a maldistribution of flow with nitroprusside in regional ischemia[87,88]; this may occur because collateral communications are in arterioles of greater than 40-micron diameter, which may be less responsive to nitroprusside than the precapillary "resistance" arterioles. Consequently, flow will increase in regions supplied by normal conductance arteries, but collateral flow from that artery may not increase despite the increase in conductance flow.

Nitrates in Congestive Heart Failure

The nitrovasodilators are extremely effective in acute and chronic congestive heart failure.[89,90] The capacity to reduce arterial and venous tone permits a reduction in afterload and preload. Reduced arterial resistance diminishes impedance to left ventricular ejection, which results in reduced left ventricular end-systolic volume. This reduction in residual volume results in a decrease in end-diastolic volume. The net effect of reducing left ventricular volume is a reduction in mitral regurgitation because of improved mitral valve and chordal-papillary geometry; and a reduction in left ventricular wall tension. This brings the required wall tension back toward a balance with the capacity of the ventricle to develop that tension as predicted by the law of Laplace (tension = pressure × left ventricular radius). This effect also reduces oxygen demand, which may diminish subendocardial ischemia and consequently improve subendocardial contractile performance.

The reduction in impedance to ejection has been thought to play a role in decreasing mitral regurgitation as well, although the transventricular gradient may not change substantially with nitrovasodilator therapy.[91] Despite a reduction in arterial resistance, arterial pressure may not decrease, depending on the effect on stroke volume. Also, even if the systolic aortic root pressure does decrease, the left atrial

TABLE 2.—*Effects of Nitroprusside and Nitroglycerin on Hemodynamic and Ventricular Function in Acute Myocardial Infarction Complicated by Heart Failure*†*

Hemodynamic or Cardiac Index	*Control*	*Vasodilator Treatment*	
		Nitroprusside	*Nitroglycerin*
Mean arterial pressure, mm of mercury	95±10	82±13‡	90±15
Pulmonary capillary wedge pressure, mm of mercury	30±7	18±4‡	18±5‡
Cardiac index, liter • min^{-1} • m^2	2.0±0.5	2.3±0.6	2.5±0.9‡
Stroke work index, grams • m^{-1} • m^2	20.3±9.3	20.4±8.0	25.2±9‡§
Systemic vascular resistance, dynes • s^{-1} • cm^{-5}	1,694±560	1,339±303	1,462±442
Global ejection fraction‖	30±8	34±9	36±6
Regional ejection fraction of infarct zone	24±7	26±6	32±6§

*From L. M. Noble, MD, J. Tillisch, MD, and G. Wisenberg, MD, et al, unpublished data, 1988.
†Data represent the mean ± standard error of the mean for 12 patients.
‡Compared with control, $P<.05$.
§Compared with nitroprusside treatment, $P<.05$.
‖Determined by radionucleotide equilbrium blood pool scan.

TABLE 3.—*Hemodynamic Effects of Nitroprusside and Sublingual Isosorbide Dinitrate in Severe Chronic Heart Failure*†*

Hemodynamic Index	*Control*	*Treatment*	
		Nitroprusside	*Sublingual Isosorbide Dinitrate*
Mean arterial pressure, mm of mercury	96±4	89±3	89±6
Heart rate, bpm	95±3	91±4	92±4
Pulmonary capillary wedge pressure, mm of mercury	30±2	19±1‡	20±2‡
Cardiac index, liters • min^{-1} • m^2	2.3±0.1	2.7±1‡	2.6±1‡
Stroke work index, grams • m^{-1} • m^2	22±2	30±2‡	32±4‡
Systemic vascular resistance, dynes • s^{-1} • cm^{-5}	1,546±100	1,265±74‡	1,389±88‡

*Modified from Kovick et al.[75]
†Data represent the mean ± standard error of the mean for 12 patients.
‡Compared with control, $P<.05$.

pressure may decrease in parallel, leaving the transventricular gradients unchanged.

In summary, the effects of nitrovasodilators in severe heart failure are to improve cardiac output and reduce left ventricular filling volume and therefore pressure, with minimal effect on the mean arterial pressure (Table 3). Nitroprusside, with balanced arterial and venous effects, is of greatest use in the initial treatment of severe heart failure. Nitroglycerin and isosorbide dinitrate, however, which have simplistically been classified as predominantly venodilators, are statistically indistinguishable in hemodynamic targets, despite a slightly lesser arterial vasodilating capacity (Tables 2 and 3). Clinically we have found that nitroglycerin is less effective as a vasodilator in patients with chronic hypertension.

Clinical Use of Nitrates

Nitroglycerin and its analogues have been shown to be effective in various clinical circumstances:

Acute myocardial infarction. The early intravenous use of nitroglycerin decreases mortality[92] and infarct size[93] and may diminish left ventricular deformation by reducing myocardial wall stress. The nonparenteral use of nitrates in the acute and subacute phases of myocardial infarction offers similar benefits, but the ability to titrate carefully and the lack of important drug tolerance with intravenous nitroglycerin commend the intravenous route with dosages from 60 to 200 μg per minute. The maximum coronary artery vasodilating effect may occur at intermediate doses, but greater arterial vasodilating occurs with the higher doses.

Unstable angina. Nitroglycerin remains a mainstay of anginal therapy. Again, intravenous administration permits a more rapid and sustained effect. Presumably the relative lack of drug tolerance with the intravenous route relates to the higher levels of drug obtained, although some tolerance occurs.[94] In unstable angina, efforts at diminishing platelet adherence and fibrin clot with aspirin and heparin are critical adjuncts to attempts at dilating the lesion and available collaterals with nitroglycerin.

Stable angina. Silent ischemia, often without substantial physical activity, occurs more frequently than does symptomatic angina in patients with stable angina. In addition, some patients seem to be unable to manifest angina despite substantial ischemia. Whether treating silent ischemia is beneficial remains controversial, but with symptomatic or silent ischemia, nitrate therapy can be most effective when dosing coincides with maximal ischemic risk. Constant nonparenteral nitrate therapy, even if possible, seems to promote drug tolerance. Intermittent dosing before exertion and other potentially ischemia-inducing activity seems satisfactory. Isosorbide dinitrate given at six to eight intervals with one longer drug-free interval when ischemia is least likely, or nitroglycerin patches or ointment, again with a drug-free interval of 8 to 12 hours, is effective in controlling symptoms, even if not in totally abolishing all ischemia.

Congestive heart failure. Nitroprusside as the initial therapy for acute cardiac decompensation offers several advantages.[95] First, its short duration of action permits more aggressive titration of the drug to improve maximal cardiac output. Second, the balanced arterial and venous effects result in clinical improvement from diminished impedance to ejection and lesser preload stress. Last, the most appropriate relation between stroke volume, filling pressure, blood pressure, and vascular resistance can be rapidly determined to serve as a target for subsequent oral "unloading" therapy. Doses between 40 and 200 μg per minute are used, with hemodynamic titration. Nitroglycerin is an effective alternative in most patients; those with a history of hypertension or severe vasoconstriction may be refractory. Nitroglycerin doses in patients in heart failure usually range between 150 and 200 μg per minute.

Isosorbide dinitrate given in doses of 30 to 80 mg every six to eight hours provides adequate arteriodilation and venodilation in chronic nonischemic heart failure.[75] Nitroglycerin topically has been less useful, probably because of practical dose limitations, although nitroglycerin ointment may occasionally be better tolerated than isosorbide dinitrate. Mild heart failure may respond to lesser doses of nitrates, but effective diuresis may obviate the need for nitrates in such patients.

Nitrovasodilators are effective agents in ischemic and nonischemic cardiac disease. Individual titration of doses to a physiologic end point, objectively determined, has expanded the use of these agents, whereas arbitrary dose limits have resulted in less therapeutic response. Consideration of the interplay between myocardial oxygen supply and demand, ventricular filling pressure and volume-dependent wall stress, impedance to ejection, and adequate arterial perfusion permits the use of these agents for the maximal therapeutic benefit.

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Overview of Osteoporosis

B. LAWRENCE RIGGS, MD, *Rochester, Minnesota*

Osteoporosis is defined as an absolute decrease in the amount of bone to a level below that required for mechanical support or, as Fuller Albright succinctly put it many years ago, "There is too little bone" (Figure 1). The bone that is present is normal chemically and histologically.

Epidemiology

Osteoporosis is a major public health problem[1,2] In the United States, about 1.5 million fractures are attributable to osteoporosis each year. The sites of these fractures are the vertebrae (650,000), the hip (250,000), the distal forearm (Colles' fracture, 200,000), and other skeletal sites (400,000). One third of women over age 65 at some time will suffer vertebral fractures; the lifetime risk for hip fracture in white women, 15%, approximates that of the combined risks of breast, endometrial, and ovarian cancer. The lifetime risk of hip fracture in men, 5%, approximates that of the risk of prostate cancer. The direct and indirect costs of osteoporosis in the United States have been estimated to be $7 billion to $10 billion annually. Much of this expense relates to hip fracture. This catastrophic type of injury is fatal in 12% to 20% of cases. Half of the survivors are unable to walk unassisted, and 25% are confined to long-term care in a nursing home.

Pathophysiology

Age-Related Bone Loss. It is convenient to divide the skeleton into two compartments consisting of cortical bone and trabecular bone. Cortical bone predominates in the shafts of long bones; trabecular bone is concentrated in the vertebrae, in the pelvis and other flat bones, and at the end of long bones. Trabecular bone is metabolically much more active than cortical bone, probably because of its greater surface area, and is more responsive to changes in mineral homeostasis.

Three distinct phases of changes in bone mass over life can be recognized, two of which occur in both sexes and one third of which occurs only in women[3,4] (Figure 2). The first process leads to attainment of peak bone mass and represents the summation of growth (90% to 95%) and consolidation (5% to 10%).[4] Peak bone mass is attained both by linear growth due to mineralization of the endochondrial growth plates and by radial growth due to a rate of periosteal apposition that exceeds that for endosteal resorption. After closure of the growth plate about age 20, the radial growth continues for another 10 to 15 years.

The second process consists of a slow, age-dependent phase of bone loss. This begins around age 40 for cortical bone and perhaps 5 to 10 years earlier for trabecular bone and continues into extreme old age.[1,3] The rate of slow bone loss due to this process probably is similar in men and women and results in losses of similar amounts of cortical bone and of trabecular bone.[1,3,5] In women, a third process, a transient accelerated postmenopausal phase of bone loss due to estrogen deficiency, is superimposed on the slow phase of bone loss and results in loss of disproportionately more trabecular bone than of cortical bone.[1,3,6,7] The amount of bone that is lost over life with each of these phases is not well defined. However, a reasonable estimate is that the slow phase produces a loss of about 25% from the cortical compartment and about 25% from the trabecular compartment in both sexes. During the accelerated phase, postmenopausal women lose an additional 10% from the cortical compartment and 25% from the trabecular compartment. Thus, overall, women lose about 35% of cortical bone and 50% of trabecular bone during their lifetime, whereas men lose about two thirds of these amounts.[1,5,8]

Age-Related Changes in Bone Remodeling. Bone formation and bone resorption occur at anatomically discrete foci called bone remodeling units.[1,4] At the beginning of each remodeling cycle, through a mechanism yet to be defined, flattened lining cells are activated and retract to expose the underlying bone.[9] Osteoclast precursor cells in marrow are recruited and migrate to the exposed area of bone. These fuse to form osteoclasts and, over a period of 1 to 3 weeks, the osteoclasts construct a tunnel in cortical bone or a lacuna on the surface of trabecular bone. The osteoclasts disappear during a reversal phase and are replaced by osteoblasts, which then fill in the resorption cavity over a period of 3 to 4 months to create a new structural unit of bone (Figure 3).

The main determinant of the rate of bone turnover is the frequency of activation of new bone remodeling units.[4,10] In normal young adults, the processes of bone resorption and bone formation are tightly coupled so that bone balance is maintained. However, during age-related bone loss, there is a remodeling imbalance with a relative or absolute increase in resorption over formation.[4,10] Because of this imbalance at each bone remodeling unit, an increase in bone turnover (i.e., an increase in the number of bone remodeling units) leads to increased bone loss.

The slow and accelerated phases of bone loss are associated with two different abnormalities of bone remodeling (Figure 4). In the slow, age-dependent phase, the osteoclasts construct resorption cavities of normal depth, or even decreased depth, but the osteoblasts fail to refill them completely.[1,4,5] This leads to a gradual thinning of the trabeculae,

(Riggs BL: Overview of osteoporosis. West J Med 1991 Jan; 154:63-77)

Mayo Clinic and Mayo Medical School, Rochester.

Dr Riggs is Consultant, Division of Endocrinology and Metabolism, Mayo Clinic, and Purvis and Roberta Tabor Professor of Medical Research, Mayo Medical School, Rochester, MN 55905.

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Reprint requests to B. Lawrence Riggs, MD, Department of Medicine, Mayo Clinic, Rochester, MN 55905.

but their connectivity is maintained.[1,11] In contrast, the accelerated, postmenopausal phase of bone loss is associated with a high rate of bone turnover; there is an increase in osteoclast number and the osteoclasts create a resorption cavity of increased depth (Figure 4). These processes lead to trabecular perforation and loss of structural trabeculae and trabecular connectivity.

Age-Related Fractures. When the incidence of fractures is plotted as a function of age, two distinct patterns emerge.[1,12] (Figure 5). The first pattern involves fractures at sites containing large amounts of trabecular bone, such as the distal forearm (Colles' fracture) and vertebrae. These fractures increase in women soon after menopause; for Colles' fracture, the incidence continues to increase until age 65 when it reaches a plateau, whereas the incidence of vertebral fractures continues to rise. The second pattern involves sites containing similar amounts of cortical and trabecular bone. Although the most important fracture of this type involves the hip, a similar pattern is followed by fractures of the proximal humerus, proximal tibia, and pelvis. The incidence of these fractures increases quite slowly with aging until late in life, when an exponential increase leads to a very high incidence of fracture. Fractures of the shafts of the limb bone, which is predominantly cortical bone, do not increase with aging and often are associated with severe trauma; therefore, they do not seem to be directly related to osteoporosis.

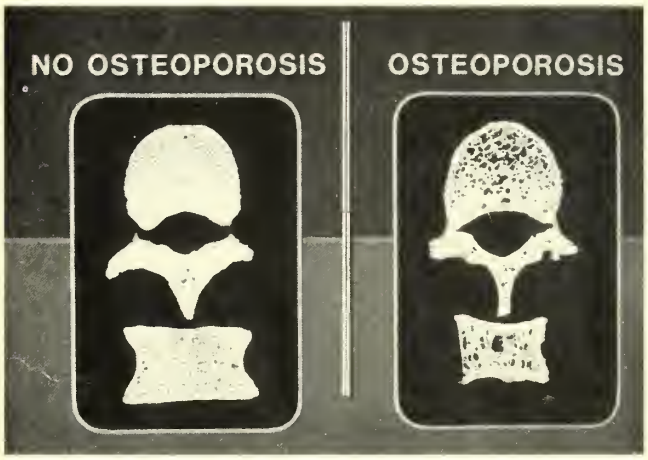

Figure 1.—Transverse and coronal sections or vertebrae from normal and osteoporotic subjects. (From Riggs BL: Osteoporosis. *In* DeGroot LJ et al (Eds): Textbook of Endocrinology. 2nd Ed. Philadelphia, W. B. Saunders Company, 1989, pp 1188-1207.)

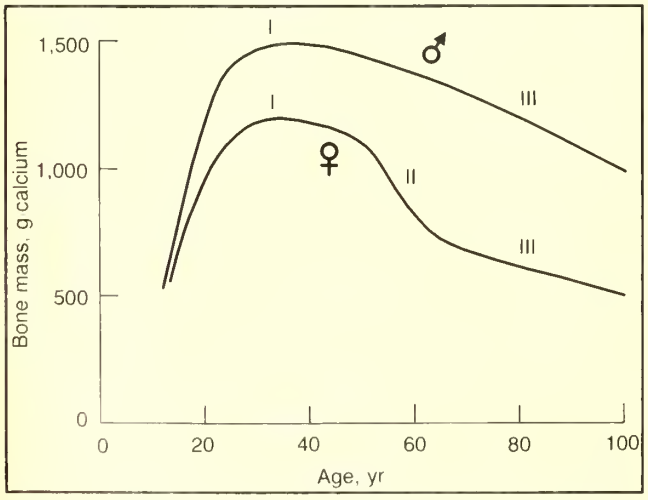

Figure 2.—Changes in bone mass with growth and aging in men and women, showing three distinct phases. See text for details. (From Riggs BL: Involutional osteoporosis. *In* Williams TF, Evans JG (Eds): Oxford Textbook of Geriatric Medicine. London, Oxford University Press, in press.)

Etiology

The modern concept is that osteoporosis is a multifactorial disorder. Figure 6 gives a model for the main groups of these factors and how they interact. The morbid event in osteoporosis is fracture. This results from the interaction of low bone density and trauma. Low bone density later in life can occur because the amount of peak bone mass achieved by young adulthood is inadequate or because there is an increased rate of bone loss. The major groups of factors causing increased bone loss can be subsumed under the categories of aging, menopause, local factors regulating bone turnover, and sporadic factors occurring in some but not other members of the population.

Low Bone Density

A decrease in bone mass clearly is the most important cause of fractures in osteoporosis. Eighty per cent of the variance in compressive strength of the trabecular bone and 90% of that in cortical bone can be accounted for by differences in bone density.[3] In the absence of severe trauma, fractures do not occur until bone density has fallen below the

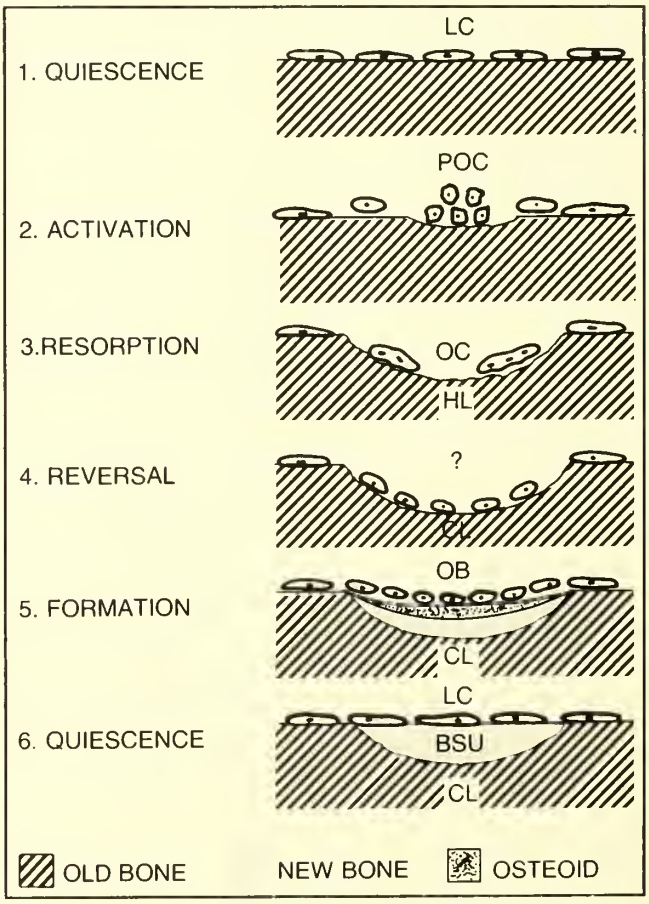

Figure 3.—Illustration of the different stages of bone remodeling. See text for details. (From Parfitt AM: Bone remodeling: Relationship to the amount and structure of bone, and the pathogenesis and prevention of fractures. *In* Riggs BL, Melton LJ III (Eds): Osteoporosis: Etiology, Diagnosis, and Management. New York, Raven Press, 1988, pp 45-94.)

values found in young adults.[5] This fracture threshold has been empirically set at about 1.0 gm per sq cm for the vertebrae, 1.0 gm per sq cm for the proximal femur, and 0.4 gm per sq cm for the ultradistal radius.[13,14] With further decreases in bone density below the fracture threshold, the incidence of hip fractures, vertebral fractures, and Colles' fractures increases. Thus, the lower the level of bone density, the greater the risk of fracture. These increases, however, are not linear, which suggests that osteoporosis may lead to qualitative changes in bone that may weaken the skeleton. Possible qualitative changes include loss of structural elements and trabecular connectivity, accumulation of trabecular microfractures, and, in some elderly subjects, histologic osteomalacia.[15]

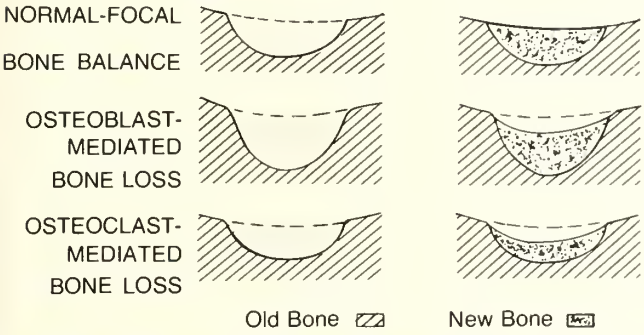

Figure 4.—Two mechanisms for remodeling imbalance in trabecular bone. In healthy young adults **(upper panel)**, the osteoblasts completely refill the resorption cavity constructed by the osteoclasts. In osteoclast-mediated bone loss **(middle panel)**, a resorption cavity of excessive depth is shown that is incompletely refilled by a normal amount of new bone. In osteoblast-mediated bone loss **(lower panel)**, there is a resorption cavity of normal depth that is incompletely filled by a subnormal amount of new bone. (From Parfitt AM: Bone remodeling: Relationship to the amount and structure of bone, and the pathogenesis and prevention of fractures, *In* Riggs BL, Melton LJ III (Eds): Osteoporosis: Etiology, Diagnosis, and Management. New York, Raven Press, 1988, pp 45-94.)

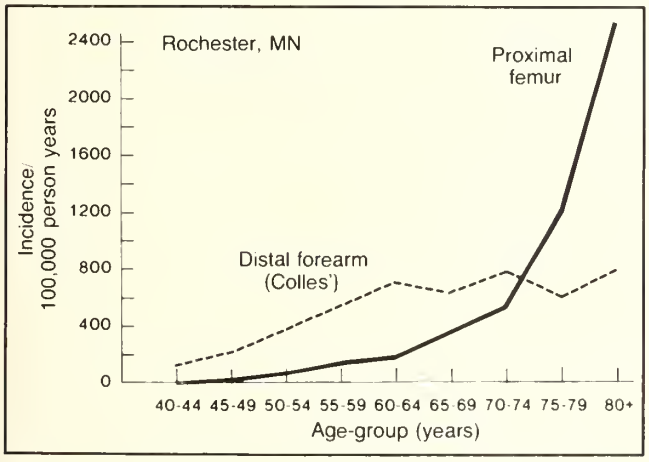

Figure 5.—The two major age-related fracture patterns, as illustrated by the incidence of Colles' fracture and hip fracture as a function of age in women residing in Rochester, MN. (From Riggs BL, Melton LJ III: Evidence for two distinct syndromes of involutional osteoporosis. Am J Med 1983; 75:899.)

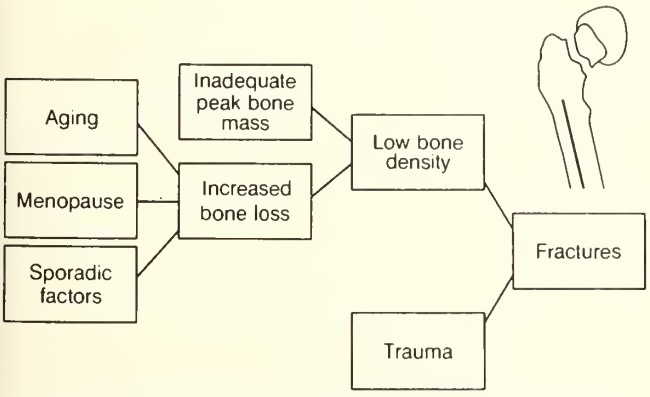

Figure 6.—Model for etiology of osteoporosis showing various groups of factors causing fractures and their interaction.

Trauma

The propensity of the elderly to fall is an independent risk factor for fractures.[16,17] The most common cause of fractures among elderly persons is a simple fall from a standing height or less, although a few hip fractures may be spontaneous and vertebral fractures often result from lifting or straining. The risk of falling increases with aging, and at least one third of community-dwelling elderly persons fall at least once each year. Falls are more frequent in the elderly because of failing vision, neurologic diseases and their sequelae or arthritis of the lower limb joints, and the use of sedatives and other drugs.

Also, the elderly have increased trauma in their falls because impaired coordination and slowed reflexes reduce their ability to break the impact of a fall. In addition, the type of fall may determine the site of fracture.[17,18] Forward falls in which the impact is broken by the outstretched hands are more likely to result in distal forearm (Colles') fracture, and a backward fall landing on the buttocks or with a lateral fall landing on the hip are more likely to result in proximal femur fracture. Although the elderly fall frequently, only 6% of their falls result in fracture.[19]

Inadequate Peak Bone Mass

Insufficient accumulation of bone during skeletal growth and consolidation predisposes to fractures later in life as age-related bone loss ensues. Differences in peak bone mass may explain in part racial and sexual differences in the incidence

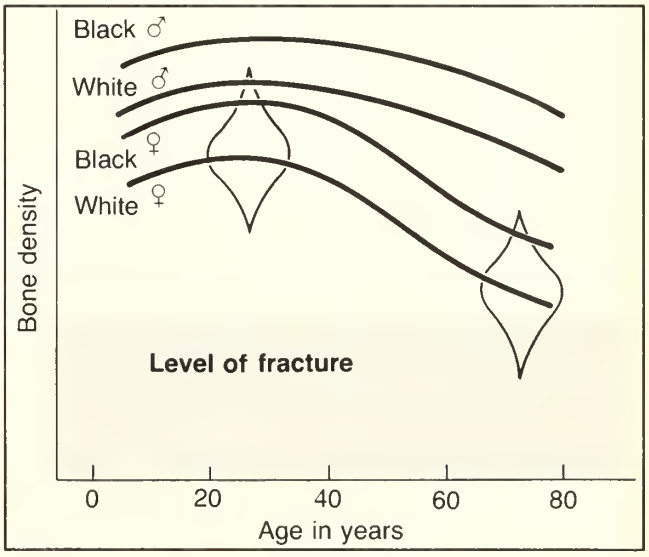

Figure 7.—Effect of sex and race on peak bone mass can explain susceptibility to osteoporosis as age-related bone loss ensues. Individual values about regression lines (for white women this is given by a top-shaped figure). Thus, a white woman in the lower part of the normal distribution in young adult life would be at increased risk for fractures later in life. (From Riggs BL: Osteoporosis, *In* DeGroot LJ, et al (Eds): Textbook of Endocrinology, 2nd Ed. Philadelphia, WB Saunders Company, 1989, pp 1188-1207.)

of osteoporosis.[20] White women have the lightest skeletons and black men have the heaviest; white men and black women have skeletons of intermediate density (Figure 7). This rank order corresponds to the rank order for the occurrence of fractures. Women of short stature and northern European extraction tend toward a more gracile skeleton and also have an increased incidence of osteoporosis later in life. Moreover, if the rate of bone loss with age is constant, those white women with the lowest peak bone mass are at greatest risk for fractures later in life[21] (Figure 7).

Although the determinants of differences in peak bone mass among individuals have not been adequately defined, two important factors appear to be heredity and the level of dietary calcium consumption during growth. Peak bone mass has strong genetic determinants, and studies in monozygotic and dizygotic twins have found a heritability index of about 0.85[22,23] (Figure 8). This may explain the trend for familial aggregation of osteoporosis.[24] It is obvious that insufficient calcium intake will be rate limiting for accumulation of skeletal mass; this is consistent with epidemiologic findings.[25]

Increased Bone Loss

Age-Related Factors. By far the most powerful predictor of bone mass in a given individual is age. For example, if the age of a healthy woman is known, the bone density of her lumbar spine or femoral neck can be predicted with a standard deviation of only 10%[5] (Figure 9). The decrease in bone density with age probably reflects the aggregate effects of a number of age-related factors.

One important factor is decreased osteoblast function. This abnormality, which can be assessed by measurement of wall thickness of trabecular packets, begins in middle life and becomes progressively more severe as age increases.[4,27] Although impaired osteoblast function could be caused by senescence, fracture healing in the elderly is not delayed, indicating that osteoblasts do respond to appropriate stimuli. More likely, the regulation of osteoblast activity is impaired by altered production of systemic or local growth factors. For example, circulating levels of growth hormone and insulin-like growth factor I (IGF-I, somatomedin C), which mediates the effect of growth hormone in bone and cartilage, both decrease by almost one half with aging.[27,28] Moreover, bone cells synthesize and respond to a number of regulators of cell proliferation—especially IGF-I, IGF-II, and transforming growth factor β.[29,30] The production of or response to one or more of these growth factors could decrease with aging.

A second age-related factor is a decrease in intestinal transport of calcium which occurs in both sexes, particularly after age 70[31,32] (Figure 10). The main regulator of calcium absorption is the physiologically active metabolite of vitamin D, 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$]. Both a decrease in the responsiveness of the intestine to $1,25(OH)_2D_3$ and a decrease in the production rate of $1,25(OH)_2D_3$ may contribute to the decrease in calcium absorption. Although available data are conflicting, the largest study showed that serum $1,25(OH)_2D_3$ concentration increased until age 65 and then decreased.[33] An increase in serum $1,25(OH)_2D_3$ associated with a concomitant decrease in calcium absorption suggests a primary impairment in intestinal responsivess to $1,25(OH)_2D_3$ action. In experimental animals, the concentration of $1,25(OH)_2D_3$ receptors in both intestine and bone cells decreases with aging.

The activity of the renal enzyme 25-hydroxyvitamin D [25(OH)D] 1α-hydroxylase, which is responsible for the conversion of 25(OH)D to $1,25(OH)_2D_3$, is impaired with aging.[34,40] This abnormality may result from atrophy of renal parenchymal tissue with aging and probably decreases the production of $1,25(OH)_2D_3$ in the elderly, especially in those whose glomerular filtration rate is <40 mL per min. This late-occurring defect aggravates the impairment in calcium absorption caused by intestinal resistance to $1,25(OH)_2D_3$.

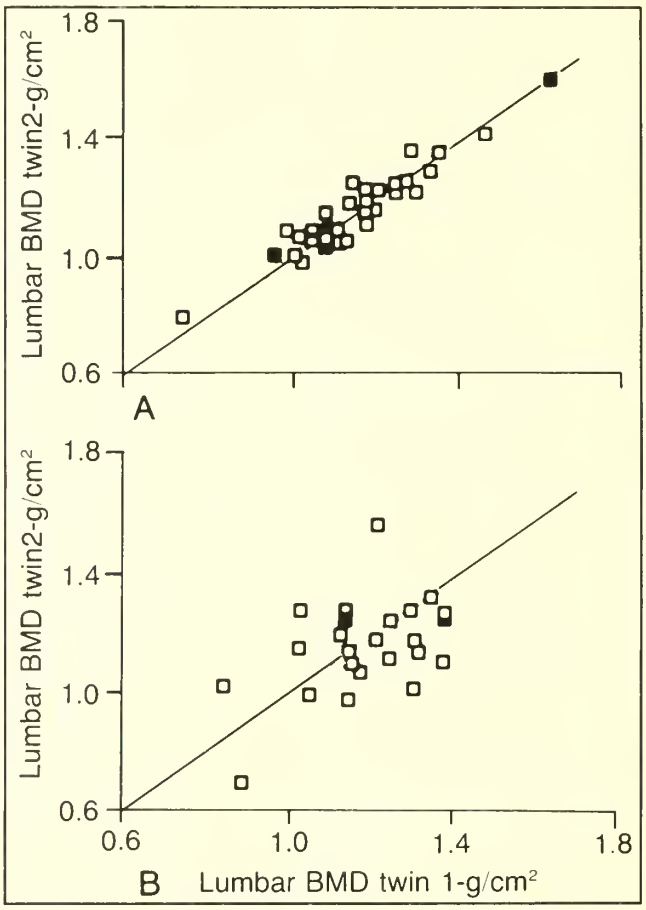

Figure 8.—Relationship between density of lumbar spine in monozygous **(upper panel)** and dizygous **(lower panel)** twin pairs. Diagonal represents line of identity. Note that agreement is much better for the monozygous twins. (From Pocock NA, et al: Genetic determinants of bone mass in adults. A twin study. J Clin Invest 1987; 80:706.)

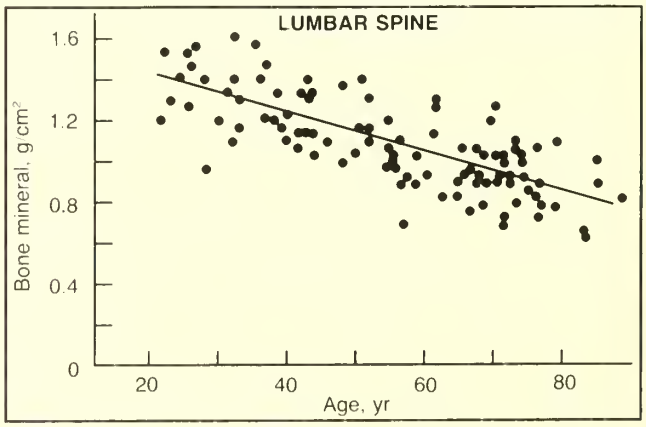

Figure 9.—Relationship between age and density of the lumbar spine in 105 normal women. (From Riggs BL, et al: Differential changes in bone mineral density of the appendicular and axial skeleton with aging: Relationship to spinal osteoporosis. J Clin Invest 1981; 67:328.)

Thus, because they absorb calcium poorly, elderly individuals should consume more calcium to maintain calcium balance, but in fact they consume less. Although the RDA for calcium is 800 mg per day, the recent NHANES survey by the US Public Health Service showed that two thirds of middle-aged and elderly women surveyed had an intake of only 550 mg per day, and one third had an intake of <400 mg per day.[32]

If the decrease in calcium absorption in the elderly is physiologically important, it should induce a compensatory secondary hyperparathyroidism and increased bone loss. There is evidence that both of these events occur. Serum immunoreactive parathyroid hormone (iPTH) increases with aging: increased circulating intact PTH in the elderly has now been convincingly demonstrated by NH_2-terminal-specific radioimmunoassay,[36] by PTH bioassay,[37] and by immunoradiometric assay (unpublished data). Further, in contrast to the older belief that bone turnover decreases with aging, data obtained with biochemical markers for bone turnover, such as serum osteocalcin and serum bone alkaline phosphatase,[38] and with tetracycline-based bone histomorphometry[39] show that it increases. The increase in bone turnover results in an increased number of bone remodeling units, and because of the remodeling imbalance between resorption and formation due to impaired osteoblast function, this leads to increased bone loss.

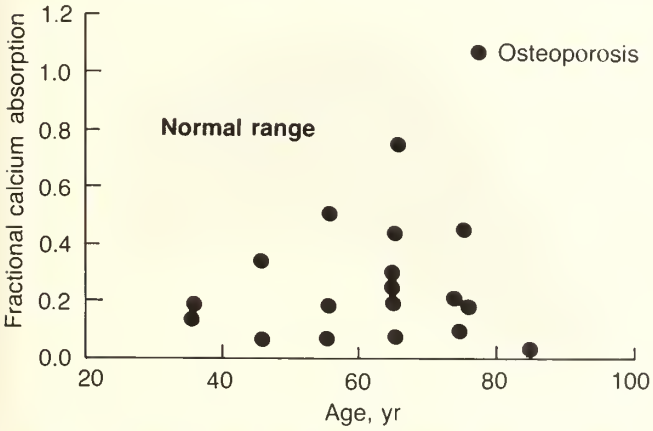

Figure 10.—Shaded area shows age-adjusted normal range for calcium absorption (assessed with ^{45}Ca and 20 mg calcium carrier) in women and closed circles indicate osteoporotic women. Note the striking reduction after age 60 years. (From Nordin BEC: Clinical significance and pathogenesis of osteoporosis. Br Med J 1971; 1:571.)

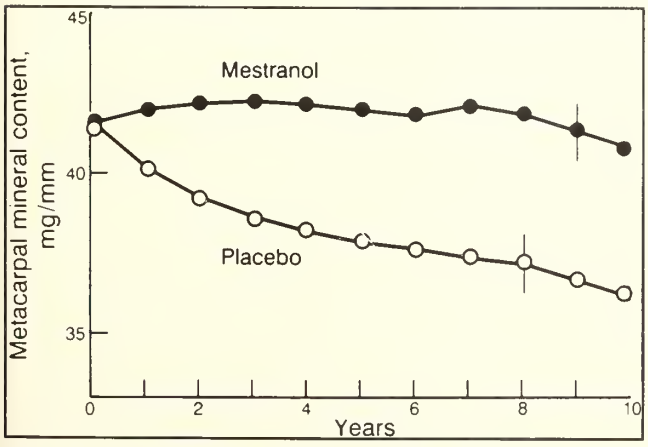

Figure 11.—Effect of estrogen or placebo treatment on bone loss after oophorectomy. (From Lindsay R, et al: Prevention of spinal osteoporosis in oophorectomised women. Lancet 1980; 2:1151.)

A third factor is an age-related decrease in serum 25(OH)D.[40] Aging decreases absorption of vitamin D from the intestine and the dermal synthesis of vitamin D following solar exposure.[41] In addition, many of the elderly are housebound and poorly nourished. A relative or absolute deficiency of vitamin D could contribute to impaired calcium absorption and to bone loss. Indeed, about 10% of elderly American patients having bone biopsy at the time of orthopedic surgery following hip fracture have histologic osteomalacia.[42]

Menopause. Surgical menopause accelerates bone loss, and estrogen replacement prevents or slows this loss in both the appendicular and axial skeletons[6,16] (Figure 11). Postmenopausal administration of estrogen decreases the occurrence of subsequent vertebral or hip fractures by about 50%.[43,44] Women who have undergone oophorectomy in young adulthood have lower bone density in later life than do non-oophorectomized premenopausal women of the same age.[45] Thus, estrogen deficiency at the menopause is an unequivocal cause of bone loss and subsequent fractures in women. Although men do not undergo the equivalent of menopause, male hypogonadism is often associated with osteoporosis.[46]

The accelerated phase of postmenopausal bone loss lasts for about 5 to 10 years,[6] but a component of bone loss up to 20 years after menopause may be related to estrogen deficiency.[47] Normal human bone cells contain sex steroid receptors and respond directly to treatment with these steroids.[48]

Sporadic Factors. A variety of behavioral and environmental factors may increase the rate of bone loss in a given individual. Smoking and high alcohol consumption increase the risk for developing osteoporosis by twofold, and their effects are additive.[49] Ethanol is toxic to osteoblasts.[50] Obesity is protective,[49] possibly because of increased loading stress to the spine and, in postmenopausal women, because of increased conversion (in fat tissue) of adrenal androgens to estrogens.

Skeletal loading from weight bearing and skeletal stresses from muscle contraction stimulate osteoblast function. Muscle mass and bone mass are directly related.[51] Among amen-

TABLE 1.—*Classification of Clinical Types of Osteoporosis*

Primary osteoporosis	Bone marrow disorders
Juvenile	Multiple myeloma and related disorders
Idiopathic (young adults)	Systemic mastocytosis
Involutional osteoporosis	Disseminated carcinoma
Endocrine diseases	Connective tissue diseases
Hypogonadism	Osteogenesis imperfecta
Ovarian agenesis	Homocystinuria
Hyperadrenocorticism	Ehlers-Danlos syndrome
Hyperthyroidism	Marfan's syndrome
Hyperparathyroidism	Miscellaneous causes
Diabetes mellitus (?)	Immobilization
Gastrointestinal diseases	Chronic obstructive pulmonary disease
Subtotal gastrectomy	Chronic alcoholism
Malabsorption syndromes	Chronic heparin administration
Chronic obstructive jaundice	Rheumatoid arthritis (?)
Primary biliary cirrhosis	
Severe malnutrition	
Alactasia	

orrheic anorexic women, those who are more physically active have denser bones than those who are sedentary.[52] Regular exercise programs retard bone loss in postmenopausal women.[53]

Nutritional factors also may be important, although there is considerable controversy regarding this. Inadequate calcium intake may be particularly important during skeletal growth in obtaining the maximal bone mass and, because of inadequate calcium absorption, in maintaining bone mass in the elderly. In a study of older men and women, the level of calcium intake at entry was found to be inversely related to the occurrence of hip fractures when the group was reassessed after 14 years.[54] Nonetheless, a community-based longitudinal study[55] failed to demonstrate a relationship between dietary calcium intake and rates of bone loss. Thus, there is considerable uncertainty whether calcium intake plays much of a role in young or middle-aged adults, except for those with very low intakes (<400 mg per day).

Clinical Spectrum

A classification of the clinical types of osteoporosis is given in Table 1. Osteoporosis can be either primary or secondary, depending on the absence or presence of concurrent medical diseases, surgical procedures, or medications known to be associated with osteoporosis. Such secondary causes can be identified in 20% of women and 40% of men presenting with vertebral fractures[1] and should always be searched for.

Idiopathic Juvenile Osteoporosis

A rare, self-limited primary form of the disease occurs in boys and girls, usually between the ages of 8 and 14 years.[56] The disease runs an acute course, usually over a period of 2 to 4 years, and then remits. During the active phase of the disease, there is growth arrest and multiple axial and appendicular fractures. The clinical severity of the osteoporosis runs the spectrum from mild to severe. The most striking feature of the disease is its almost invariable spontaneous remission with resumption of normal linear and radial bone growth.

The etiology of this condition is obscure. Although the close relationship of the disease to puberty has led some to speculate that hormonal factors are important, there have been documented cases of onset and remission of the disease well before puberty.

Diagnostically, it is important to exclude other causes of osteopenia in children, including Cushing's syndrome, acute leukemia, and osteogenesis imperfecta.

Idiopathic Osteoporosis in Young Adults

This is much more common than idiopathic juvenile osteoporosis but still is much less frequent than involutional osteoporosis. In contrast to involutional osteoporosis, which occurs predominantly in women, idiopathic osteoporosis occurs in both sexes with equal frequency. Undoubtedly, idiopathic osteoporosis represents a composite of several etiologically distinct disorders. The clinical spectrum varies widely: sometimes it is mild and is clinically manifested by a single or only a few vertebral fractures, even in the absence of treatment. More commonly, however, there are multiple vertebral fractures occurring over a period of 5 to 10 years with associated loss of height of up to 6 inches. In contrast to involutional osteoporosis, fractures of the ribs and metatarsals are common. In severely affected patients, there may be unilateral or bilateral hip fractures.

TABLE 2.—*The Two Clinical Types of Involutional Osteoporosis*

	Type I	*Type II*
Age, yr	51-75	>70
Sex ratio, F:M	6:1	2:1
Type of bone loss	Mainly trabecular	Trabecular and cortical
Rate of bone loss	Accelerated	Not accelerated
Main fracture sites	Vertebral (crush) and distal radius (Colles')	Vertebral (multiple wedge and hip)
Main causes	Factors related to menopause	Factors related to aging

Serum values for calcium, phosphorus, and alkaline phosphatase are normal. Hypercalciuria is relatively common and is associated with normal values for serum $1,25(OH)_2D_3$.[57] Bone histomorphometry after tetracycline double labeling has shown both high and low bone turnover forms.

Involutional Osteoporosis

Involutional osteoporosis can be divided into two distinctive syndromes on the basis of differences in clinical features, hormonal changes, and the relationship of the disease patterns to age and menopause.[1,58] This concept may prove helpful in clinical assessment, in examining the pathogenesis of the disease, and in evaluating therapy (Table 2).

Type I (Postmenopausal) Osteoporosis. This syndrome characteristically affects women within 15 to 20 years after menopause and results from an exaggeration of the postmenopausal phase of accelerated bone loss. Although a clinically similar form of osteoporosis may occur in men of the same age, this may represent the same process diagnosed in younger men as idiopathic osteoporosis but occurring at an older age. Type I osteoporosis is characterized by a disproportionate loss of trabecular bone which results in fractures at skeletal sites with a high concentration of trabecular bone, especially in the vertebrae, at the distal forearm (Colles' fracture), and at the distal ankle. The vertebral fractures usually are the "crush" type and are associated with considerable deformation and with pain.

The rate of trabecular bone loss in patients with type I osteoporosis is two to four times greater than that of postmenopausal women of the same age without fractures, but the rate of cortical bone loss is only slightly greater. There is some controversy regarding the characteristics of bone turnover, which has variously been reported to be high, normal, or low following analysis of tetracycline-labeled iliac biopsy samples. In a large recent series that employed histomorphometric methods allowing the assessment of both bone formation and bone resorption rate, bone turnover was increased in one third of patients but was normal in the remainder.[59] The increase in bone formation, however, was less than the increase in bone resorption, leading to a remodeling imbalance and bone loss. This remodeling imbalance is consistent with an osteoblast defect, which was demonstrated histologically by a decrease in wall thickness. There was a continuum in changes in bone turnover between the normal and high bone turnover patients rather than a bimodal distribution. Although the possibility of subtypes exists, it is more likely that

some osteoporotic patients have passed through a high turnover stage and have reached a stage of normal bone turnover in which further loss of trabecular bone will be small.

Type I osteoporosis appears to be caused by factors that are closely related to or are exacerbated by menopause. This leads to the following cascade: accelerated bone loss, decreased secretion of parathyroid hormone and increased secretion of calcitonin, and functional impairment in 25-hydroxyvitamin D [25(OH)D] 1α-hydroxylase activity with decreased production of $1,25(OH)_2D_3$, therefore leading to decreased calcium absorption. The defect in calcium absorption may further aggravate bone loss.

All women are estrogen deficient after menopause, however, and serum levels of sex steroids are similar in postmenopausal women with and without type I osteoporosis.[60] Thus, other factors must augment the rate or the duration of the accelerated phase of bone loss: these factors interact with estrogen efficiency to determine individual susceptibility. One possible mechanism is defective regulation of osteoblast function that could account for the impaired bone formation detected by histomorphometry.[59] Thus, when bone turnover increases as a consequence of the menopause, those women who are destined to develop type I osteoporosis compensate less well for the increase in bone resorption by increasing bone formation. Another possible mechanism is local elaboration of a factor that potentiates the effect of estrogen deficiency on increasing bone resorption. Patients with type I osteoporosis and high bone turnover have increased production of interleukin-1 by stimulated monocytes as compared with age-matched controls.[61] This increase can be normalized by treatment with estrogen.[62] On a motor basis, interleukin-1 is the most potent factor known to increase bone resorption. Another possible mechanism is increased sensitivity of bone to circulating PTH, although a recent study infusing PTH into normal and osteoporotic postmenopausal women could not document this.[63] A final possible mechanism is that those persons entering the menopause with low-normal values for bone density may be the first whose values fall below the fracture threshold as postmenopausal bone loss ensues. This is unlikely to be the major mechanism, however, because compared with age-matched postmenopausal controls, most patients with type I osteoporosis have increased rates of bone loss.[64] Obviously, these possibilities are not mutually exclusive.

Type II (Age-Related) Osteoporosis. This syndrome occurs in both men and women age 70 and older but is twice as common in women. It results from slow bone loss operating over a period of several decades. The main manifestations are fractures of the hip and vertebral fractures, although fractures of the proximal humerus, proximal tibia, and pelvis are common. The vertebral fractures are often of the multiple wedge type, leading to dorsal kyphosis ("dowager's hump"). Trabecular thinning associated with slow bone loss is responsible for the gradual and usually painless vertebral deformation. In type II osteoporosis, bone density values for the proximal femur, vertebrae, and sites in the appendicular skeleton are usually in the lower part of the normal range (adjusted for age and sex). This suggests proportionate losses of cortical and trabecular bone and a rate of loss that is only slightly higher than the mean for age-matched peers. Thus, the age-related processes causing type II osteoporosis appear to affect virtually the entire population of aging men and women, and, as the slow phase of bone loss progresses, an increasing number of them will have bone density values below the fracture threshold.[21] The two most important of these age-related factors are decreased osteoblast function and decreased calcium absorption with secondary hyperparathyroidism.

Secondary Osteoporosis

Endocrine Diseases. Osteoporosis may be associated with a number of syndromes of endocrine dysfunction. Hypogonadism in either sex increases the incidence of osteoporosis. Hypogonadism is probably the main cause of osteoporosis associated with ovarian agenesis (Turner's syndrome), although a genetic abnormality of bone maturation probably also is present. Functional hypogonadism in female distance runners may be associated with decreased vertebral density.[65] Endogenous or exogenous hyperadrenocorticism both decreases bone formation and increases bone resorption with rapid bone loss. The decrease in bone formation results from inhibition of collagen biosynthesis. The increase in bone resorption may be indirectly mediated, possibly by an increased sensitivity of bone to parathyroid hormone. Patients with glucocorticoid excess also have impaired calcium absorption, and this can be reversed by administering vitamin D or its active metabolite. An effect of corticosteroids on vitamin D metabolism, however, has not been conclusively established.

Hyperthyroidism consistently increases bone turnover, but in most patients formation and resorption remain coupled. Symptomatic osteoporosis associated with hyperthyroidism, therefore, is relatively unusual and, when present, generally occurs in postmenopausal women. Osteitis fibrosa is the characteristic skeletal abnormality associated with hyperparathyroidism; nevertheless about 5% of patients, mostly postmenopausal women, present with osteopenia and vertebral compression fractures. In contrast, mild hyperparathyroidism in younger subjects is not associated with bone loss.[66] Patients with either juvenile- or adult-onset diabetes mellitus may have an increased risk for osteoporosis, but this has not been clearly established. Osteoporosis associated with acromegaly is believed to be rare and, when present, is the result of concomitant hypogonadism. In fact, because of the anabolic effect of growth hormone excess on the skeleton, most patients with acromegaly have an increase in both trabecular and cortical bone mass.

Gastrointestinal Diseases. These conditions can cause either osteoporosis or osteomalacia, and they generally produce a mixture of both. About 5% of patients with subtotal gastrectomy, particularly those with the Billroth II type, subsequently develop bone disease. Malabsorption syndromes impair absorption of calcium and vitamin D; usually this results in osteomalacia. However, if this is mild, the predominant lesion may be osteoporosis. Chronic obstructive jaundice may be associated with bone disease because the enterohepatic circulation of active vitamin D metabolites is impaired. This mechanism may play a role in the osteomalacia associated with primary biliary cirrhosis. In the United States, however, osteoporosis associated with a profound depression in bone formation is the typical finding.[67] Its etiology is unknown. Severe malnutrition involving both protein and calcium deficiency—as has been observed in prisoners of war—may cause osteoporosis. Women with anorexia nervosa often have osteoporosis, with functional amenorrhea also possibly contributing to the bone loss. Finally, alactasia has

been reported in up to 30% of osteoporotic subjects. This disorder may be a risk factor for osteoporosis because it produces intolerance to milk and thus is associated with a low calcium intake.

Bone Marrow Disorders. Multiple myeloma produces diffuse osteoporosis in about 10% of patients and other myeloproliferative disorders may do so less frequently. This abnormality is mediated by an increased local production of lymphotoxin, interleukin-1, or other cytokines by bone marrow cells. Diffuse osteoporosis also may occur when disseminated carcinoma involves the bone marrow.

Connective Tissue Diseases. An unusually severe form of osteoporosis may occur in osteogenesis imperfecta. This disease is usually inherited as an autosomal dominant trait and is associated with blue sclera, deafness, thin skin, and impaired biosynthesis of type I collagen. Several types of mutations or deletions of the gene for type I procollagen have been described in patients with this phenotype. Although onset usually is in childhood, some patients present with premature spinal osteoporosis in the absence of a history of limb bone fracture. The Marfan and Ehlers-Danlos syndromes also may be associated with spinal osteopenia but less frequently include vertebral fractures. Osteoporosis commonly occurs in patients with homocystinuria, an autosomal recessive disorder caused by deficient cystathionine synthase activity. The resultant increase in homocysteine and other metabolites in the circulation interferes with cross-linking of collagen.

Miscellaneous Causes. Total immobilization, such as occurs in traumatic quadriplegia, results in a loss of up to 1% of bone per month, especially in the trabecular bone of the axial skeleton. After loss of 40% to 50% of bone from the spinal column, a new steady state is reached and bone mass is maintained. Bone loss is associated with both depressed bone formation and enhanced bone resorption. Significant bone loss also occurs during total bed rest among nonparalyzed individuals and in astronauts during gravitational weightlessness. If immobilization is transient, replacement of bone mass occurs on remobilization, provided that there has been only thinning of bone trabeculae rather than loss of trabeculae and other structural elements.

Not infrequently, osteoporosis is associated with chronic obstructive pulmonary disease. Whether this is related to the consumption of tobacco, which is believed to be a bone toxin, or to the pulmonary disease itself is unknown. Young alcoholics also have been shown to have thinner bones than other

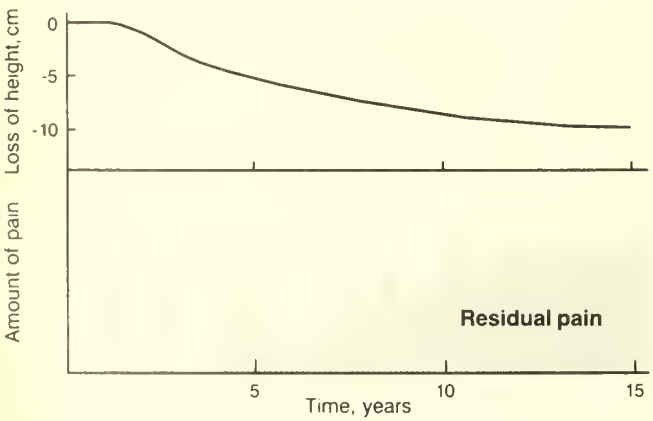

Figure 12.—Clinical course of an untreated or unsuccessfully treated patient with osteoporosis. Upper panel shows continued loss of height. Lower panel shows occurrence of back pain which is at first acute and intermittent but later chronic.

subjects of similar age. Long-term therapy with heparin has been reported to cause severe loss of bone and spontaneous fractures. Heparin decreases the stability of lysosomes, and release of collagenase and other lysosomal enzymes may be responsible for the bone loss. Whereas it has been suggested that osteoporosis may be a complication of rheumatoid arthritis, most of the bone loss in these patients can probably be accounted for by use of corticosteroids and by immobilization.

Clinical Presentation

Osteoporosis is manifested by back pain, loss of height, spinal deformity (especially kyphosis), and fractures of the vertebrae, hips, wrists, and, less frequently, other bones. The most characteristic symptom of osteoporosis is back pain caused by vertebral compression. Typically, a woman within 20 years after menopause develops acute lumbar or thoracic back pain after some ordinary activity such as raising a window or lifting a sack of groceries. The pain may be mild or severe, and it may be localized or radiate to the flank. It remits in days or weeks but then recurs with the occurrence of new fractures. After several episodes of acute, intermittent pain, a chronic mechanical backache may develop as a result of spinal deformity (Figure 12). In untreated or unsuccessfully treated patients, severe kyphosis may develop with a loss of 4 to 8 inches in height. In severe cases, the rib cage comes to rest on the pelvic brim, The frequency of occurrence of vertebral fractures and the number of fractures that eventually occur vary widely among patients, but the average is one per year in the initial phase of the disease. In general, progression is slower in elderly women, and commonly substantial dorsal kyphosis and cervical lordosis—the so-called dowager's hump—develops in the absence of significant pain. Half of the hip fractures in elderly men and women are spontaneous and half are associated with falls.

Diagnosis

General Medical Examination

All patients with newly discovered osteoporosis should have a general medical evaluation to assess severity and to exclude secondary diseases that may cause the osteoporosis. There should be historical documentation of the chronology and location of fractures, previous treatment, age at onset and type of menopause (natural or surgical), presence of fractures or osteoporosis in other family members, presence of risk factors such as use of alcohol and tobacco, previous gastrointestinal surgery, and use of corticosteroids. Systemic symptoms of abnormal physical findings suggest the presence of an underlying disease. Even severe osteoporosis generally does not result in weakness or loss of weight.

The physical examination should include an accurate measurement of height and a search for findings suggestive of systemic disease. Blue sclera, thin skin, and lax joints may be indicative of osteogenesis imperfecta or a related collagen disorder. Characteristic physical findings of Cushing's syndrome or hyperthyroidism should be sought for. The presence of splenomegaly or hepatomegaly suggests the presence of lymphoma or other malignancy.

All patients should have a complete blood cell count, determination of erythrocyte sedimentation rate, multichannel serum chemistry analyses, and urinalysis. Serum calcium and phosphorus levels are normal in primary osteoporosis.

Serum alkaline phosphatase levels also are normal except for transient elevations during healing of vertebral fractures. Sustained elevations of the alkaline phosphatase level, in the absence of liver disease, suggest osteomalacia or skeletal metastases.

Multiple myeloma may be present without symptoms and with a normal hematogram and erythrocyte sedimentation rate. Although most cases can be diagnosed by serum and urine protein electrophoresis, bone marrow examination may be required to establish the diagnosis. Bone marrow examination is sometimes also necessary to diagnose the presence of disseminated carcinoma.

Radiologic Findings

Radiographs of the spinal column should be obtained in all patients to diagnose vertebral fracture as a cause of back pain, to evaluate severity of the underlying osteoporosis, to provide a baseline for assessing the effect of therapy on future fracture occurrence, and to search for evidence of secondary diseases that may have produced the osteoporosis. Generalized osteopenia is suggested by the findings of accentuation of the vertebral end plates, prominence of the weight-bearing vertical trabeculae (due to disappearance of the horizontal trabeculae), and loss of contrast in radiodensity between the interior of the vertebral body and the adjacent soft tissue. Vertebral deformity may take the form of collapse (reduction of anterior and posterior height), anterior wedging (reduction in anterior height, usually occurring in the thoracic spinal column), or "ballooning" (by concave compression of the end plates resulting from pressure of the intervetebral disk, usually occurring in the lumbar spinal column). Also, the nucleus pulposus may herniate locally into the vertebral body (Schmorl's nodes). The severity of the osteoporosis may be defined as follows:[68] two Grade I fractures, mild osteoporosis; three to five Grade I or one or two Grade II fractures, moderate osteoporosis; and more than this, severe osteoporosis (Figure 13). A radiograph of the spinal column in a typical patient with osteoporosis is shown in Figure 14B.

Osteoporosis due to glucocorticoid excess should be considered when there is associated osteoporosis of the skull, fractures of the ribs and pelvic rami, and prominent partially mineralized callus at the site of fracture. In the absence of pseudofractures, osteomalacia may be difficult to distinguish from osteoporosis, but it often has a radiographic "ground glass" appearance rather than the characteristic "clear glass" appearance of osteoporosis. Posterior wedging of a vertebra (except for L-5) suggests a destructive lesion rather than osteoporosis.

Bone Densitometry

Recent development of methods that allow precise measurement of bone mineral density in the axial skeleton at sites subject to fracture represents a major advance in the care of osteoporotic patients.[69,70] These measurements have three principal uses: (1) to confirm the diagnosis of osteoporosis, (2) to estimate the severity of bone loss, and (3) to determine whether the patient is responding to treatment. The characteristics of the available three techniques are compared in Table 3. Single-energy quantitative computed tomography (QCT) can be performed using commercially available CT scanners and a calibration phantom. Reproducibility is satisfactory but accuracy is poor (mainly because of a confounding effect of marrow fat), and radiation exposure is relatively high. Better accuracy can be obtained with dual-energy QCT, but at the price of poor reproducibility and higher radiation exposure. Nonetheless, the method is quite sensitive (because of its ability to measure exclusively the metabolically active trabecular bone in the center of the vertebral body) and specific (because distortion by extravertebral artifacts is avoided). Dual-photon absorptiometry (DPA) uses transmission scanning with a ^{153}Gd source that emits two photoelec-

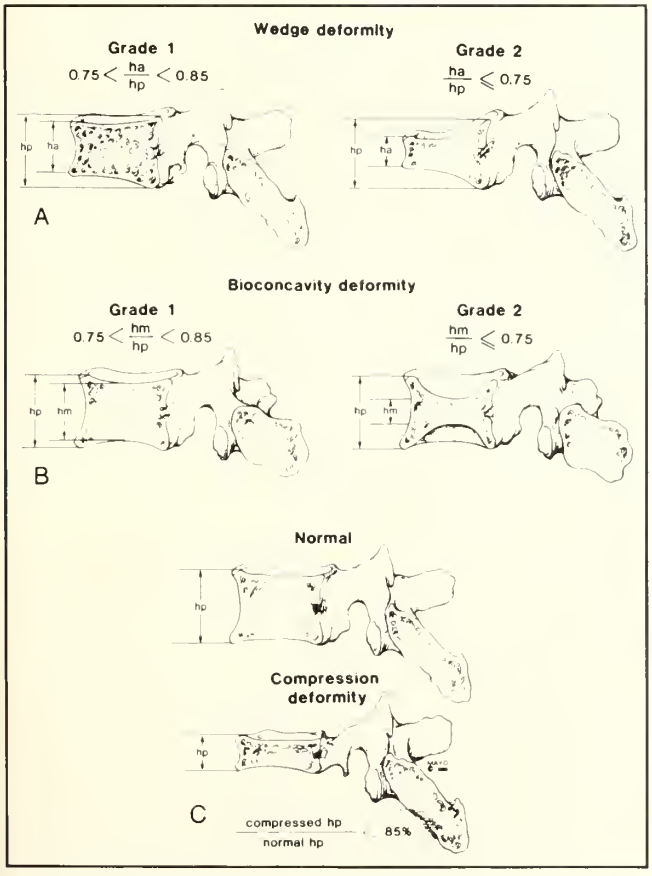

Figure 13.—Method for staging severity of vertebral fractures. See text for details. (From Eastell R, Riggs BL: Diagnostic evaluation of osteoporosis, *In* Young WF, Klee GG (Eds): Endocrinol Metab Clin North Am. Philadelphia, WB Saunders Company, 1988, pp 547-571.)

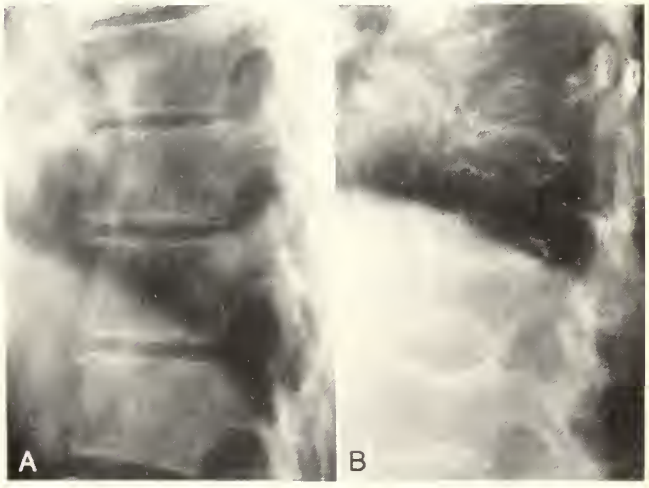

Figure 14.—Radiographs of the spinal column. **A,** Normal bone in a 60-year-old woman. **B,** Vertebral osteoporosis in a 62-year-old woman. There is a decrease in bone density with high-grade collapse fractures of T-12 and L-1 and ballooning (expansion of the intervertebral discs) of L-2 and L-3.

TABLE 3.—*Major Methods for Measuring Bone Mineral Density of the Axial Skeleton*

	QCT	DPA	DEXA
Reproducibility, %	3-5	2-4	1-2
Accuracy, %	5-15	4	4
Radiation, mrems	300-500	5-10	<5
Scan time, min	10-20	30	10

tric peaks, thereby allowing bone density to be measured independently of soft tissue thickness and composition. The method has good reproducibility and accuracy and low radiation exposure, but it measures the entire vertebra, which is only 70% trabecular bone, and results are affected by the presence of dystrophic calcification, osteoarthritis of the spinal column, and vertebral compression fractures within the scanning area. The most recently developed technique is dual-energy x-ray absorptiometry (DEXA), which also utilizes dual-energy transmission scanning but generates photons from an x-ray tube rather than from an isotope source.[71] The new method has several important advantages over DPA, including better reproducibility, shorter scan time, and a scan image approaching that of a standard skeletal radiograph in quality. In contrast to QCT, both DPA and DEXA are capable of measuring mineral density of the proximal femur and of the total skeleton.

Bone density of the appendicular skeleton can be measured by single-photon absorptiometry using transmission scanning with a ^{125}I source. Although the method has good reproducibility (1% to 3%), the correlation between density of the lumbar spine and the radius or os calcis is too low ($r = 0.5$ to 0.8) for vertebral density to be predicted accurately in individual patients. Thus, these older methods gradually are being replaced by QCT, DPA, and DEXA.

Assessment of Bone Turnover

Measurement of bone turnover is helpful in management of the osteoporotic patient in two ways. First, as discussed later, it may be helpful in deciding which type of treatment to employ. Osteoporotic patients with high bone turnover are likely to have a good response to antiresorptive therapy whereas those with low turnover are not. This distinction will become increasingly more important as effective formation-stimulating regimens are developed. Second, it is useful in following the course of therapy.

Iliac trephine biopsy may be useful in selected patients for this purpose and also may be used to exclude osteomalacia.[4] Biopsy specimens should be obtained after the patient has received tetracycline double-labeling. (Tetracycline is selectively deposited in areas where there is bone formation, and it fluoresces when the bone section is transilluminated with ultraviolet light). The biopsy specimen should be processed by an experienced laboratory that will provide quantitative information.

The other way to assess bone turnover is by biochemical markers.[72] Alkaline phosphatase is produced by osteoblasts. Although total serum alkaline phosphatase is relatively insensitive, measurement of the specific isoenzyme of bone may be helpful. Another marker reflecting bone formation is serum bone Gla-protein (BGP, osteocalcin). BGP is a noncollagenous protein found only in bone and dentin. Circulating levels can be measured by radioimmunoassay and correlate well with bone histomorphometry-based measurements of bone formation. Unfortunately, a sensitive measure for bone resorption is not available. Urinary hydroxyproline excretion is relatively insensitive and difficult to measure and requires dietary control to obtain reliable results. Recent reports, however, suggest that urinary excretion of specific pyridinium crosslinks may be a highly specific and sensitive measure of bone collagen breakdown.[73]

A diagnostic algorithm for investigation of the patient with osteoporosis is shown in Figure 15.

Treatment

General Therapeutic Measures

Acute back pain responds to analgesics, heat, and general massage to alleviate muscle spasm. Sometimes a brief period of bed rest is required. Chronic back pain often is caused by spinal deformity and thus is difficult to relieve completely. Instruction in posture and gait training and institution of regular back extension exercises to strengthen the flabby perivertebral muscles are generally beneficial. Occasionally, use of an orthopedic back brace is required. All patients with osteoporosis should have a diet adequate in calcium, proteins, and vitamins, should be reasonably active physically, and should take precautions to prevent falls.

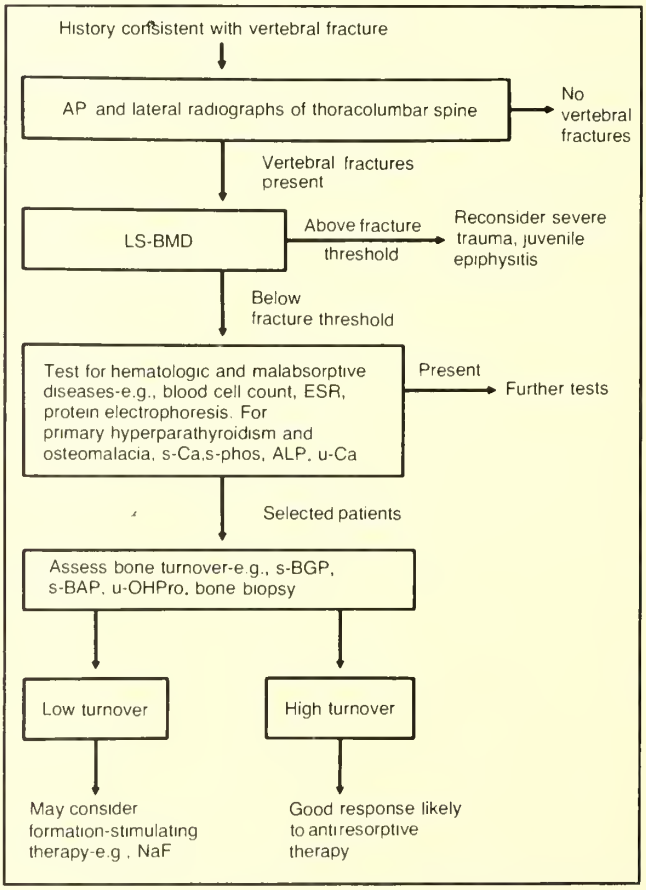

Figure 15.—Diagnostic algorithm for investigation of the patient with osteophorosis. ALP=alkaline phosphatase; AP=anteroposterior; S-BAP=serum bone specific alkaline phosphatase; S-BGP=serum bone Gla-protein; S-Ca=serum calcium; u-Ca=urinary calcium; ESR=erythrocyte sedimentation rate; uOHPro=urinary hydroxyproline; LS-BMD=dual-photon absorptiometry of the lumbar spine. (From Eastell R, Riggs BL: Diagnostic evaluation of osteoporosis, *In* Young WF, Klee GG (Eds): Endocrinol Metabol Clin North Am. Philadelphia, WB Saunders Company, 1988, pp 547-571.)

Drug Therapy

General Considerations. The drugs in the treatment of osteoporosis can be classified as antiresorptive or formation-stimulating (Figure 16). Because of the tight coupling between bone resorption and bone formation, when the new steady state is attained after 3 to 6 months of treatment, there also is a decrease in bone formation that approximates the decrease in bone resorption.[4] Thus, the best result that can be obtained with this class of therapeutic agents is maintenance of existing skeletal mass or slowing of the rate of bone loss. Nonetheless, the rate of new fractures will be decreased by antiresorption therapy because bone structure will be stabilized and thus not subject to further weakening by continued bone loss.[4] In contrast, therapeutic programs that stimulate bone formation more than bone resorption have the potential for increasing bone mass substantially and thus of eliminating the risk of new fractures.

Most of the currently available drug regimens act by inhibiting bone resorption. The antiresorption drugs include calcium, estrogen, calcitonin, vitamin D and 1,25-dihydroxyvitamin D ($1,25[OH]_2D_3$), and, probably, anabolic steroids. The regimens that primarily act by stimulating bone formation include sodium fluoride, low intermittent dosage of parathyroid hormone (PTH), combined phosphate and calcitonin, growth hormone and insulin-like growth factor I, and the AFDR regimen (coherence therapy). Of these various therapeutic regimens, only estrogen and calcitonin have been approved for treatment of established osteoporosis by the United States Food and Drug Administration. Calcium is considered a nutritional supplement and can be sold without prescription. The remaining regimens are investigative and should not be used for the routine treatment of osteoporosis.

Calcium. Calcium supplementation seems to have at least a modest effect on retarding bone loss and reducing fractures in osteoporosis. Relatively large doses may be required, 1,000 to 1,500 mg of supplementary elemental calcium daily; calcium may act by decreasing PTH secretion. Further, it is safe, well tolerated, and inexpensive. Of the various calcium salts, calcium carbonate is most widely used and has the advantage that elemental calcium represents 40% of its total weight. However, calcium carbonate may produce gaseousness and constipation in some patients, and for this reason, calcium citrate or calcium phosphate may be used as alernative preparations. Generally, it is best to give the calcium supplements in divided doses, with meals and at bedtime.

Estrogen. After calcium, estrogen is the most widely prescribed drug for the treatment of established osteoporosis in the United States. As with other antiresorptive drugs, its effectiveness varies directly with the level of bone turnover, being most effective when it is high and least effective when it is low. Estrogen acts directly on bone cells to reduce bone resorption and may oppose the action of PTH. The therapeutic dosage of estrogen in the treatment of osteoporosis is 0.625 to 1.25 mg of conjugated estrogen daily or its equivalent in another estrogen preparation. Estrogen should be given cyclically, such as 25 out of 30 days, and a progestin such as medroxyprogesterone acetate, 5 to 10 mg daily, should be given for the last 14 days of the cycle. This will prevent the development of endometrial hyperplasia and, presumably, endometrial carcinoma, which has a 5- to 10-fold increase in incidence when unaccompanied estrogen is

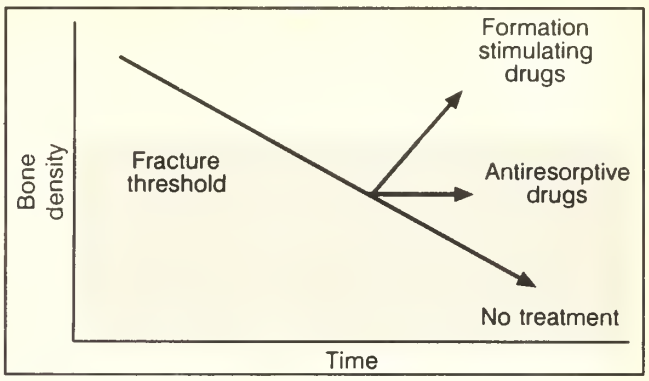

Figure 16.—Effect of two major types of drugs on bone density in a hypothetical patient with osteoporosis.

given to postmenopausal women.[74] Because of the high concentration of estrogenic substances in the portal vein following oral administration, the liver produces increased amounts of coagulation factors, renin substrate, and bile cholesterol.[74] These increases probably account for the increased incidence of venous thrombosis and pulmonary embolism, hypertension, and gallstones, respectively, in postmenopausal women receiving estrogen in moderate to high dosages. These complications can be largely avoided by administering estrogen by transdermal patch.[75] Estrogen improves the serum lipid profile in postmenopausal women and may decrease the incidence of coronary artery disease; these favorable effects, however, may be largely offset when a progestin is administered concurrently. Whether estrogen therapy results in a small increase in risk for breast cancer is still uncertain.[76] Nonetheless, annual breast examination and mammography must be done during treatment. Other untoward effects that may occur in some subjects include menorrhagia, metrorrhagia, fluid retention, and edema.

Calcitonin. Calcitonin, a 32-amino acid polypeptide secreted by the C cells of the thyroid gland in response to an increase in plasma calcium, acts directly on the osteoclasts, which contain calcitonin receptors. Thus, it may substitute for estrogen as an antiresorptive drug. Moreover, in contrast with estrogen, side effects are minor.

Nonetheless, calcitonin has several disadvantages. First, the drug must be made synthetically and is very expensive. Second, it requires parenteral administration. (Recently, however, a transnasal preparation[77] has been developed by several pharmaceutical companies. It is presently available in Europe for treatment of patients and is undergoing clinical testing in the United States.) Third, a substantial proportion of patients treated with salmon calcitonin will develop resistance after one or more years of treatment. Part of this resistance is caused by development of circulating neutralizing antibodies, a complication that is more likely to occur after salmon calcitonin than after human calcitonin administration, but other mechanisms also appear to be operative.

The usual dose is 100 MRC units of salmon calcitonin or 0.5 mg of human calcitonin subcutaneously daily or on alternate days, at bedtime. Calcium supplements should be given as 1 to 2 g of elemental calcium in divided doses to prevent secondary hyperparathyroidism, which may occur when calcitonin is given alone.

Short-term calcitonin therapy increases total body calcium modestly, as assessed by neutron activation analysis. When patients receiving calcitonin treatment for postmeno-

pausal osteoporosis were stratified on the basis of bone turnover (assessed by whole body retention of ^{99m}Te-methylene diphosphonate), however, the normal turnover subgroup neither gained nor lost a significant amount of bone mineral, whereas the higher turnover subgroup increased lumbar spine bone density (assessed by QCT) by 22% with one year of treatment.[78] Thus, as with estrogen therapy, the response to treatment was proportional to the activity of the disease.

Vitamin D and 1,25-Dihydroxyvitamin D. Currently, the major reason for using vitamin D or $1,25(OH)_2D_3$ in the treatment of osteoporosis is to correct low intestinal calcium absorption. Pharmacologic dosages of vitamin D (10,000 U per day or more) are required to overcome the defect in calcium absorption found in patients with osteoporosis. By contrast, only physiologic dosages (0.5 to 0.75 μg per day) of the active metabolite, $1,25(OH)_2D_3$, are required. Thus, osteoporotic patients may have impaired conversion of vitamin D to $1,25(OH)_2D_3$. Also, $1,25(OH)_2D_3$ may have a trophic action on osteoblasts, which contain $1,25(OH)_2D_3$ receptors, but a direct therapeutic effect on osteoblasts has not been established.

Data on the efficacy of $1,25(OH)_2D_3$ in the treatment of osteoporosis have been conflicting, some showing but some failing to show a beneficial effect on bone turnover or on rates of bone loss.[64,79] In general, results have been better when patients with more severe osteoporosis have been treated, particularly when there is evidence of impaired calcium absorption. A recent two-center study showed that patients receiving $1,25(OH)_2D_3$ therapy had a better than 50% reduction in the number of new vertebral fractures as compared with a randomized group receiving placebo.[80]

Because $1,25(OH)_2D_3$ is the final product of vitamin D metabolism and is not subject to feedback control, there are significant risks of hypercalcemia and hypercalciuria when it is used therapeutically. Earlier concerns about renal damage, however, have not been substantiated when patients are carefully followed. Nonetheless, the dosage of $1,25(OH)_2D_3$ probably should be restricted to 0.5 to 0.75 μg per day; although a dietary calcium intake of 800 mg daily should be maintained, additional supplementary or dietary calcium should be interdicted. Low-dose $1,25(OH)_2D_3$ combined with 1,000 mg per day of supplementary calcium has been reported to retard bone loss without problems of hypercalcemia.[81] Serum and urine calcium should be monitored regularly during treatment.

Biphosphonates. These compounds are structurally similar to pyrophosphate (P-O-P) except that the oxygen is replaced by carbon (P-C-P). This chemical modification makes the drugs resistant to degradation by alkaline and acid phosphatases. Biphosphonates are absorbed poorly (< 10%), but once in the circulation, they are taken up avidly by the skeleton or excreted unchanged by the kidney. In bone, they are adsorbed to the surface of hydroxyapatite crystals. Biphosphonates inhibit bone resorption, either by toxic action on the osteoclasts or by rendering hydroxyapatite more resistant to osteoclastic resorption. In addition, one agent in this class, sodium etidronate (EHDP), inhibits bone mineralization and with higher dosages or with prolonged use of low dosage may lead to osteomalacia. Another biphosphonate, dichloromethane diphosphonate (Cl_2MDP), initially showed considerable promise in the treatment of osteoporosis but was withdrawn because of possible hematologic toxicity. A third biphosphonate, amino-hydroxypyropylidine (APD), that is currently undergoing clinical trials in Europe, has been shown to increase bone mass by about 2% to 3% per year in osteoporotic women.[82] Except for transient hyperpyrexia at the initiation of treatment (due to increased production of interleukin-1) and minor gastrointestinal symptoms, the drug is well tolerated. Newer and more potent biphosphonates are currently being developed.

Anabolic Steroids. Because of virilization, androgens should not be used in the treatment of women with osteoporosis. Synthetic 17-methylated heterocyclic steroids have been developed, however, that have equivalent anabolic activity but less androgenicity. These compounds induce a modest increase in skeletal mass.[83] Although anabolic steroids have been thought to act primarily by stimulating bone formation, radiocalcium kinetic studies suggest that they may act mainly by decreasing bone resorption. Nonetheless, they may differ in their effect on bone formation rate from estrogen (which decreases it), as they may have a weak stimulatory effect on the osteoblasts. Although anabolic agents avoid the problem of estrogen stimulation, about one-quarter of women treated develop some side effects related to androgenicity. Moreover, especially when given orally, they may increase plasma cholesterol and low-density lipoprotein concentrations and induce liver dysfunction. Because of substantial side effects, the United States Food and Drug Administration has withdrawn its approval for this class of compounds, although they continue to be used in other countries.

Sodium Fluoride. Of all the formation-stimulating regimens, only therapy with sodium fluoride has been widely evaluated. The drug is a potent osteoblast mitogen and is capable of increasing bone mass substantially (Figure 17). Increases of up to 100% occur mainly in the trabecular bone

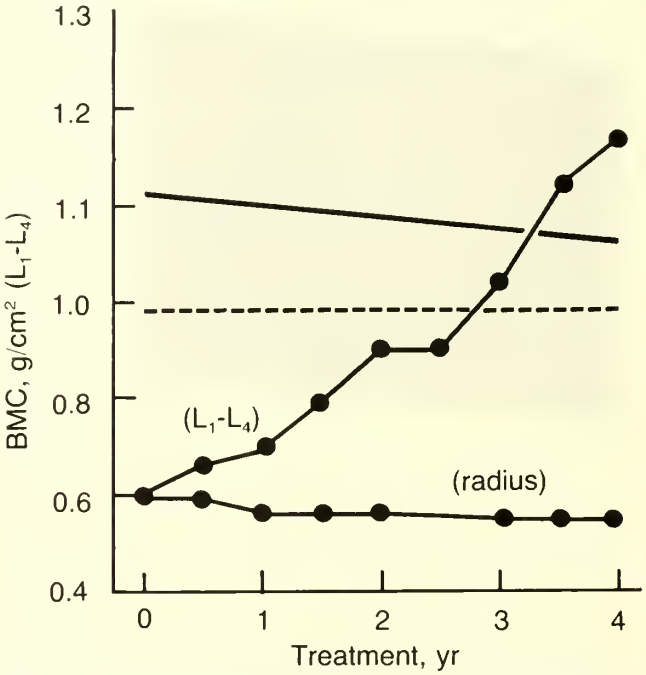

Figure 17.—Effect of sodium fluoride treatment on bone density of a 62-year-old osteoporotic woman. Cross hatched area represents normal range for bone mineral content (BMC) of lumbar spine and horizontal broken line represents fracture threshold. Note dramatic increase in BMC of lumbar spine with treatment but no change in BMC of midradius. (From Riggs et al: The role of sodium fluoride in the treatment of osteoporosis. Proceedings of the Lawrence and Dorothy Fallis Internation Symposium, Detroit, MI, May 8-13, 1988, *In* Kleerekoper M, Krane SM (Eds): Clinical Disorders of Bone and Mineral Metabolism. New York, Mary Ann Liebert, Inc., 1989, pp 605-612.)

of the axial skeleton, whereas cortical bone in the appendicular skeleton remains unchanged or decreases slightly.[84] Concurrent administration of supplementary calcium is required to offset or to minimize the incomplete mineralization that may occur when fluoride alone is given. Bone biopsy studies suggest that fluoride therapy may bypass the normal remodeling sequence and induce osteoblast formation de novo on previously quiescent surfaces.

However, fluoridic bone has increased crystallinity, decreased elasticity, and may be abnormal structurally with decreased bone strength. Recently, a two-center, randomized, controlled and double-blind study failed to demonstrate a decrease in vertebral fracture rate after 4 years of treatment with 75 mg daily of sodium fluoride.[85,86] Thus, the possibility exists that fluoride therapy induces formation of large amounts of bone that is more brittle than normal and does not result in a net increase in bone strength. Because this drug is widely used throughout the world, undoubtedly further evaluation of anti-fracture effects will be made.

Other Formation-Stimulating Regimens. Although PTH increases bone resorption, low dosage, intermittently administered PTH is anabolic and results in substantially increased trabecular bone mass.[87] This anabolic action may be mediated by local production of insulin-like growth factor-I by bone cells.[88] Combination administration of oral phosphate (to increase PTH secretion) and parenteral calcitonin (to decrease bone resorption) has also been effective in inducing moderate increases in trabecular bone short-term.[89] Finally, a theoretical approach to the treatment of osteoporosis, termed ADFR or coherence therapy, has been described in which coherent populations of bone cells are manipulated.[90] An agent such as PTH(1-34) is given to activate (*A*) remodeling cycles and to synchronize the normally asynchronous remodeling activity within the skeleton as a whole. Next, a depressing (*D*) agent such as calcitonin is given that will decrease the activity and duration of the resorption phase. This agent is then withdrawn and a free (*F*) period is allowed so that the formation period will proceed unencumbered, producing a net increase in bone mass. The cycle is then repeated (*R*). Recent studies combining intermittent cyclic etidronate have resulted in increases in bone density in the spine by 6% over 3 years compared with a placebo-treated control.[91]

Treatment of the Individual Patient With Osteoporosis

Type I (Postmenopausal) Osteoporosis. Treatment should be begun as early as possible. Thus, in patients with vertebral fractures, even mild, nontraumatic wedge fractures should be treated. Osteopenic patients without vertebral fractures but with bone density values below the age-adjusted normal range should also be treated. Patients with Colles' fracture of the distal forearm should have vertebral densitometry to determine the need for active therapy.

All patients with type I (postmenopausal) osteoporosis should receive supplementary calcium. When there is evidence of impaired calcium absorption on the basis of urinary calcium excretion of 100 mg per day or less, vitamin D or $1,25(OH)_2D_3$ should be employed. Women with more than minimal disease should receive estrogen therapy, especially when high bone turnover can be demonstrated or when patients are within 10 to 15 years past menopause. Calcitonin therapy is an alternative when estrogen therapy is contraindicated or not tolerated.

Type II (Age-Related) Osteoporosis. These patients have already lost most of the bone that they ever will lose and differ little in bone density from peers without fractures. There is no evidence that estrogen or calcitonin therapy is beneficial in such patients. Moreover, because of their age and increased incidence of asymptomatic atherosclerosis, there may be increased risk associated with estrogen therapy. Treatment consists primarily of calcium supplementation (because of impaired calcium absorption) and instruction in measures that decrease the risk of falls. The latter include use of shoes with flat heels, removal of loose floor rugs, avoidance of slippery surfaces (such as recently waxed floors or icy sidewalks), and the use of a light if it is necessary to get up from bed during the night.

Idiopathic Osteoporosis. For idiopathic osteoporosis in juveniles, the basic strategy is to protect the spine until remission occurs. Sex steroids are contraindicated because of the possibility of early closure of the growth plates. Biphosphonates or calcitonin may be useful in retarding bone loss in severely affected cases.

For idiopathic osteoporosis in premenopausal women, there is no reason to prescribe sex steroids because these patients are not estrogen deficient. The mainstay of treatment is calcium supplementation with the addition of vitamin D or its metabolites when there is evidence of impaired calcium absorption. When there is evidence of increased bone turnover, calcitonin can be added as an antiresorptive agent. Cigarettes and excess alcohol should be interdicted.

For idiopathic osteoporosis in men, the treatment is similar to that for idiopathic osteoporosis in premenopausal women. For osteoporosis occurring in older men, a careful search should be made for secondary causes, which will be found in approximately 40% of the patients. Approximately 10% to 20% of men with osteoporosis will be found to have partial or complete hypogonadism of various causes.[49] Those patients with documented low plasma testosterone levels should receive replacement therapy. Calcium supplementation, with or without pharmacologic dosages of vitamin D, is usually given also.

Osteoporosis Associated With Glucocorticoid Excess. Secondary osteoporosis is commonly caused by chronic use of pharmacologic dosages of glucocorticoids. The most important therapeutic measure is to reduce the dosage of glucocorticoids or, if possible, to discontinue it. Administration of the glucocorticoid once daily or on alternate days may maintain a more favorable balance between the anti-inflammatory and immunosuppressive effects and the osteopenic effect in some patients. All patients should receive calcium supplementation and those patients who are postmenopausal women should also be given estrogens. Although glucocorticoids inhibit calcium absorption, the use of vitamin D or its metabolites in treatment is controversial. Finally, thiazide diuretics to antagonize the calciuric effect of glucocorticoids may be useful.

Prevention of Osteoporosis

Considering the magnitude of this enormous problem, prevention is the only cost-effective approach. Dietary calcium, if low, should be increased to at least 1,000 mg per day for adults and possibly more for postmenopausal women. Increased physical activity should be encouraged, and bone toxins, such as cigarettes and heavy alcohol consumption, should be eliminated.

Of all preventive measures, however, the most effective is estrogen replacement therapy begun at menopause. A dosage of 0.625 mg per day of conjugated estrogen or its equivalent will prevent the accelerated phase of bone loss from occurring in nearly all perimenopausal women. It is not known how long estrogen therapy must be continued to be effective. Withdrawal of estrogen therapy, however, results in accelerated bone loss of the same magnitude that occurs following oophorectomy.[91] Thus, it is likely that long-term estrogen therapy will be required to gain maximal benefit.

Because of the potential adverse effects of estrogen and because of the high cost of the necessary surveillance while it is being administered, it will be necessary to develop criteria for selecting those postmenopausal women who are at greatest risk for future fracture. At present, this selection can best be made by obtaining a bone density measurement of the lumbar spine in the perimenopausal period. Those women in the top third of the age-adjusted normal distribution are at relatively low risk and need not be treated unless this is necessary for relief of menopausal symptoms. Those in the lower one third of the distribution are at increased risk, and estrogen replacement therapy should be strongly considered for them. Those in the middle one third of the distribution should have a repeat bone density measurement made after 2 to 3 years and if substantial bone loss has occurred should be reconsidered for treatment. In the future, it is possible that biphosphonate drugs may substitute for estrogen in some subjects.

Summary

Osteoporosis is a common age-related disorder manifested clinically by skeletal fractures, especially fractures of the vertebrae, hip, and distal forearm. The major cause of these fractures is low bone mass, although an increase in trauma due to falls in the elderly also contributes. There are multiple causes for the low bone mass which, in any given individual, may contribute differently to the development of the osteopenia. The most important groups of causes are failure to achieve adequate peak bone mass, slow bone loss due to processes relating to aging, the menopause in women, and a variety of sporadic behavioral, nutritional, and environmental factors that affect bone mass in some but not in other individuals. The most important approach is prevention. Drugs and behavioral factors known to cause bone loss should be eliminated and perimenopausal women should be evaluated for possible preventive administration of estrogen. For patients with fractures due to established osteoporosis, the only drugs approved by the Food and Drug Administration are the antiresorptive agents calcium, estrogen, and calcitonin. Formation-stimulating regimens, however, are being developed and may be available for clinical use in the foreseeable future. These regimens may be capable of increasing bone mass to above the fracture threshold, thereby resulting in a clinical cure of the osteoporosis.

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Management of Mild Hypertension
Selecting an Antihypertensive Regimen

Discussant
ELISEO J. PÉREZ-STABLE, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER A. BOUSHEY, MD*: *Although much remains to be learned about the pathogenesis of hypertension (see H.E. Ives, "Essential Hypertension—Where Are We Going?,"* West J Med *1990 Oct; 153:415-420), basic and applied research has laid a solid foundation for guiding clinical practice. Safe, well-tolerated medications have been shown to reduce blood pressure and the long-term risk of cardiovascular disease mortality. Most studies have been done on patients with moderate or severe hypertension, however, and the balance between the costs and benefits of therapy is not as clearly established for mild or borderline elevations in blood pressure. The equation is further complicated by the wide variety of agents available. Some of these agents appear most suitable in particular subgroups of patients. The rationale underlying the treatment of mild hypertension and for choosing an antihypertensive regimen will be reviewed by Eliseo Pérez-Stable, MD, a member of our Division of General Internal Medicine and a Henry J. Kaiser Faculty Scholar in general internal medicine.*

ELISEO J. PÉREZ-STABLE, MD†: As many as 60 million adults in the United States have a diastolic blood pressure (BP) that averages 90 mm of mercury or greater. Mild hypertension is defined as a diastolic BP of between 90 and 104 mm of mercury, a category that includes approximately 70% or 42 million of all persons with hypertension.[1] In addition, about half of all persons with mild hypertension have diastolic BPs of between 90 and 94 mm of mercury. Moderate hypertension is defined as a diastolic BP of between 105 and 114 mm of mercury and severe hypertension as a diastolic BP of 115 mm of mercury or higher.[1] In this discussion I will review the risks of hypertension, update the role of ambulatory monitoring, summarize what has been learned from clinical trials, and discuss the initial selection of antihypertensive medications.

Risks of Mild Hypertension

The relationship between blood pressure and cardiovascular disease is a continuous one. The excess risk for cardiovascular mortality begins to increase substantially at a diastolic BP of greater than 83 mm of mercury in men.[2] The selection of a uniform threshold diastolic BP at which to begin treatment with medications is arbitrary. Factors such as age, race, sex, comorbid conditions, and the presence of other cardiovascular risk factors should be considered in determining the need to treat with medications.[3] Coexisting systolic hypertension is an important factor to consider because the systolic BP has been found to be more predictive of cardiovascular disease mortality in large cohorts of British[4] and North American men.[5] Isolated systolic hypertension is found predominantly among the elderly and will not be addressed in this discussion.

The six-year coronary artery disease mortality among men 35 to 57 years of age screened for the Multiple Risk Factor Intervention Trial (MRFIT) confirms earlier reports from Framingham, Massachusetts, that having more than one cardiovascular risk factor increases the risk of dying of coronary artery disease (CAD). Although the relative risk from diastolic BPs in the mild range compared with levels below 75 mm of mercury is 2, more than 50% of all excess CAD deaths occur in these patients.[5] When these data are evaluated by cholesterol levels and smoking status, the importance of multiple risk factors is emphasized. Age-adjusted six-year CAD mortality rates per 1,000 MRFIT men are shown by risk factor categories in Table 1. Diastolic hypertension increases the risk of CAD mortality by a twofold factor in smokers and nonsmokers for each category of total cholesterol levels. The risk of CAD mortality in a nonsmoking man with hypertension is greatly increased at a cholesterol level greater than 6.31 mmol per liter (244 mg per dl). Cigarette smoking increases the risk by twofold to threefold independent of diastolic BPs and cholesterol levels. As cholesterol levels rise, the risk of CAD mortality increases by threefold from the lowest to the highest category.[5]

Between 1968 and 1988, the United States has experienced a significant reduction in the mortality rates for coronary heart disease (31.8%), stroke (45.9%), and all cardiovascular disease (33.2%) compared with a decrease of 12.8% in mortality from all noncardiovascular diseases.[6,7] Goldman and Cook have estimated that life-style factors—decreased cigarette smoking, decreased consumption of saturated fat,

*Professor and Vice-chair, Department of Medicine, University of California, San Francisco (UCSF), School of Medicine.
†Associate Professor of Medicine, Departments of Medicine and Psychiatry, UCSF.

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Reprint requests to Homer A. Boushey, MD, Department of Medicine, UCSF School of Medicine, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
BP = blood pressure
CAD = coronary artery disease
ECG = electrocardiogram
HDFP = Hypertension Detection and Follow-up Program
HDL = high-density lipoprotein
JNC = Joint National Committee on Detection, Evaluation, and Treatment of Hypertension
LDL = low-density lipoprotein
MRFIT = Multiple Risk Factor Intervention Trial
VA = Veterans Administration

healthier dietary habits, and increased physical activity—have contributed to about 50% of the decline.[8] Physician-initiated factors are estimated to account for about 40% of the decline and include the treatment and control of hypertension, the availability of coronary care units, and improved medical and surgical management of patients with cardiovascular events. Recent data from the Framingham study suggest that the decrease in the incidence of coronary heart disease is related to changes in life-style and the treatment of hypertension.[7]

The Role of Ambulatory Monitoring

The choice of 90 mm of mercury to define diastolic hypertension should not imply a fixed threshold at which to initiate therapy. Persons with readings consistently between 85 and 89 mm of mercury should be considered as having borderline diastolic hypertension, and although in most cases this does not warrant pharmacotherapy, closer follow-up and advice regarding nonpharmacologic treatment should be instituted.

Defining hypertension on the basis of office blood pressures taken by a physician or nurse with a manual sphygmomanometer is the standard used not only to collect epidemiologic data but also to evaluate the effectiveness of pharmacotherapy. In recent years studies have collected data on 24-hour blood pressure readings using ambulatory monitors. Improved technology has led to reliable and accurate readings with equipment that is practical to use. In a retrospective review of their experience, Perloff and colleagues found that among a group of patients with comparable office blood pressures, a higher average blood pressure while awake as measured by an ambulatory monitor predicted a greater risk of fatal and nonfatal cardiovascular events and had a higher correlation with the presence of left ventricular hypertrophy.[9]

TABLE 1.—*Relative Risk of Dying of Coronary Artery Disease in MRFIT Participants by Cholesterol Levels, Smoking Status, and Diastolic Blood Pressure (BP)**

Cholesterol Level		Relative Risk			
		Diastolic BP < 90 mm of mercury		Diastolic BP ≥ 90 mm of mercury	
mmol/liter	(mg/dl)	Nonsmoker	Smoker	Nonsmoker	Smoker
< 4.71	(< 182)	1.6	5.2	3.7	6.3
4.71-5.22	(182-202)	2.5	5.5	4.0	10.0
5.25-5.69	(203-220)	2.7	7.4	5.6	15.5
5.70-6.31	(221-244)	3.8	10.2	5.6	16.6
> 6.31	(> 244)	6.4	13.3	10.7	21.4

MRFIT = Multiple Risk Factor Intervention Trial

*From Kannel et al.[5]

Pickering and co-workers at Cornell University (New York City), reported that the phenomenon of "white coat hypertension" may explain as much as 20% of elevated diastolic blood pressures in the office.[10] They defined normotension on ambulatory monitoring as an average reading within the 90th percentile of a group of normal volunteers. Using this operational definition, 5% of their patients with moderate hypertension would also be considered to have white coat hypertension. In the 249 patients with mildly elevated diastolic blood pressures, thin white women were likely to have lower ambulatory blood pressures than office readings.[10] Office blood pressures are closely correlated with work-site blood pressures on ambulatory monitoring,[11] and patients who measure their own blood pressure at home with manual sphygmomanometers should also check readings in more stressful work situations. Daytime ambulatory monitoring of blood pressure is a more specific method of identifying patients with sustained hypertension. Furthermore, ambulatory monitoring may be able to identify patients at a greater risk of cardiovascular morbidity, thus meriting a more intensive treatment regimen.[12]

The routine use of ambulatory monitoring in the clinical evaluation of untreated or treated patients with hypertension is not recommended at this time. Given that currently available equipment sells for at least $5,000 and the average charges by commercial operators in the San Francisco area are $150 to $200 per recording, the role of this technology should be carefully evaluated. Currently available equipment weighs about 340 grams (12 oz) and poses little interference with routine daily activity. Although wearing the equipment and having a cuff inflate every 15 to 20 minutes are inconvenient, adverse reactions such as thrombophlebitis, edema of the hand, ecchymoses at the cuff site, exfoliative localized dermatitis, and abrasion of the antecubital fossa have been reported.[13] Ambulatory monitoring may be helpful in identifying low-risk patients with the white coat phenomenon, but multiple readings over time by different providers and self-monitoring with a manual sphygmomanometer in different settings could accomplish the same goal at a lower cost. In selected patients with medication side effects, difficult-to-control blood pressure, or other undefined circumstances, however, monitoring may provide important information.

Clinical Trials for Mild Hypertension—Lessons and Questions

Including the landmark Veterans Administration (VA) Cooperative Study Group of the late 1960s,[14] there have been eight large clinical trials evaluating pharmacotherapy for mild hypertension using control groups and four additional trials comparing two types of medications.[15] Although several questions have been answered, several others remain unsettled.

The incidence of cerebrovascular events is lowered by 33% to 100% with the use of pharmacotherapy for mild hypertension.[15] Results from the Medical Research Council trial indicate that 850 patients would need to be treated for a year to prevent 1 incidence of stroke.[16] Conversely, if all persons in this country with mild hypertension were treated and diastolic BPs were lowered by 5 to 10 mm of mercury, then approximately 50,000 cerebrovascular accidents would be prevented per year. The Centers for Disease Control estimate that hypertension accounts for 43,363 preventable deaths from stroke in the US.[17] An analysis of eight commu-

nity-based randomized trials involving more than 34,000 persons of the pharmacologic treatment of mild to moderate hypertension found that stroke incidence and mortality were reduced by an average of 40% in all studies.[18]

The incidence of morbidity and mortality from CAD has not been consistently altered in the desired direction. The MRFIT researchers found a 23% reduction in CAD mortality for participants with a normal baseline electrocardiogram (ECG) but a 68% increase in mortality for those with ECG abnormalities at baseline.[19] The MRFIT group has now reported data on a 10.5-year follow-up comparing mortality in men assigned to the special intervention with that in men having usual sources of care.[20] Mortality rates from myocardial infarction, coronary heart disease, cardiovascular disease, and all causes were lower for men receiving special intervention than those given usual care by 24.3%, 10.6%, 8.3%, and 7.7%, respectively, but only the difference for myocardial infarction was statistically significant. Mortality differences by the baseline ECG persist: the group with a normal ECG receiving special intervention had a 21.1% lower CAD mortality, but those with baseline ECG changes had a 17.8% greater CAD mortality than men receiving usual care. Men with an abnormal ECG response to exercise, however, had a 21.8% lower CAD mortality than did men receiving the usual care.[20]

The Hypertension Detection and Follow-up Program (HDFP) study compared more and free treatment (stepped-care) with less and usual-pay treatment (referred-care) and found a 16% reduction in cases of CAD and a 30% reduction in all-cause mortality.[21] The HDFP group published an 8.3-year follow-up evaluation of mortality in the randomized cohort of participants and found a persistence of a reduction in blood pressure and total mortality.[22] Although the difference in mean diastolic BPs between the stepped-care and referred-care groups was small (86.5 versus 87.8 mm of mercury), an 18% decrease in total mortality was observed. The HDFP participants in stepped-care with a baseline ECG showing left ventricular hypertrophy had a statistically insignificant ($P = .15$) 11% increase in CAD mortality, and those with normal baseline ECGs had a 36% decrease.[23]

The Australian trial found a 56% decrease in CAD mortality,[24] and the Oslo trial reported an increased ten-year CAD mortality in their treated participants (14 deaths compared with 3 deaths).[25] The Metoprolol Atherosclerosis Prevention in Hypertension Study compared the use of diuretics with that of metoprolol in white men with mild to moderate hypertension (mean entry diastolic BP, 107 mm of mercury) and showed a significant reduction in the number of cardiovascular deaths for patients on metoprolol therapy at a mean follow-up of five years (42 of 1,609 taking metoprolol versus 57 of 1,625 taking diuretics; $P = .012$).[26] The fact that the parent study (Heart Attack Primary Prevention in Hypertension) found no differences indicates that cardiovascular mortality was greater among participants taking atenolol than among those taking diuretics.[27]

The Medical Research Council trial found no overall difference in the incidence of CAD or total mortality, but subgroup analyses showed that nonsmokers treated with propranolol hydrochloride had a substantial reduction in the incidence of strokes, CAD morbidity, overall cardiovascular events, and total mortality.[16] Propranolol was not better than placebo in preventing strokes or coronary artery events among smokers. In contrast, the use of bendroflumethiazide was more effective than that of propranolol in reducing the stroke rate in both smokers and nonsmokers, but it did not reduce the rate of coronary artery events in any group.[16] These results would imply that β-blockers may be preferred therapy in nonsmokers and that smokers who are unable to quit should not receive β-blockers alone to treat hypertension. Analyses from the Heart Attack Primary Prevention in Hypertension Study, however, did not confirm these observations,[27] and caution is always warranted when evaluating subgroup analyses. Regardless, the use of cardioselective β-blockers should cause less hypertension on exposure to catecholamines such as that induced by cigarette smoke because peripheral receptors are less affected.[28] Nicotine accelerates the metabolism of propranolol, and hypertensive smokers using propranolol do not achieve the same blood pressure control as when taking other drugs.[29,30]

Cruickshank's analysis of data from six long-term studies reported in 1987 and 1988 that included a total of 14,536 men and women with mild, moderate, or severe hypertension and treated with β-blockers, diuretics, vasodilators, and central agents showed a J-shaped relation between the diastolic BP and myocardial infarction for persons with established coronary artery disease.[31] The lowest incidence of myocardial infarction was found at a diastolic BP from 80 to 91 mm of mercury, being 85 to 87 mm of mercury in four studies and 90 mm of mercury in elderly patients.[31] The J-curve relationship was present only in patients with definite ischemia and hypertension. The presumed mechanism, supported by findings in animals and humans, is that stenosed coronary arteries have a limited flow reserve and require a higher perfusion pressure.[31] If this J-curve relation is accepted, then a target range for lowering the diastolic BP should become standard practice in patients with hypertension and coronary artery disease. Alderman and associates reported a similar relationship from other risk factors.[32] They found that patients with large (average of 24 mm of mercury) decreases in diastolic BP and small (average of 5 mm of mercury) decreases in diastolic BP had a 3.8 to 4.5 greater risk of myocardial infarction compared with those with a moderate (average of 13 mm of mercury) decrease in blood pressure.[32] The stroke risk was not greater in the patients with the largest decrease in diastolic blood pressures.

The natural history of placebo-treated mild hypertension shows that a substantial number of cases remit. The Australian trial observed 1,943 placebo-treated persons with baseline diastolic BPs of greater than 94 mm of mercury, and 48% had consistent readings of less than 90 mm of mercury for the four years of study.[33] The Medical Research Council found that 18% of placebo-treated patients had a gradual reduction in diastolic BPs to levels consistently below 90 mm of mercury.[16] These data emphasize the wisdom of obtaining several readings over time before a medication regimen is recommended in uncomplicated mild hypertension. A nonpharmacologic approach to all patients with mild hypertension is recommended for at least three to six months in the absence of angina, heart failure, renal insufficiency, or other reasons mandating urgent therapy.[1] Pharmacotherapy for mild hypertension does prevent a progression to more severe hypertension, which occurred in 12% of placebo-treated subjects in the Australian study.[33] In addition, a US Public Health Service study conducted in the 1970s found that the incidence of new ECG findings of left ventricular hypertrophy and retinal changes was considerably decreased in pa-

tients treated with medications.[34] Furthermore, data from the Framingham study indicate that only a small number of pharmacologically treated hypertensive subjects experience sustained remission while not receiving medication.[35]

Controversies in Pharmacotherapy

Recommendations of the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of Hypertension have been published since 1977. The stepped-care approach to the pharmacologic treatment of hypertension was used in the HDFP and MRFIT clinical trials and has served as the guideline for thousands of practitioners. The proportion of persons who are aware of and are being treated for hypertension and whose hypertension is controlled has also increased substantially.[36] The 1984 JNC report recommended the use of β-blockers as an alternative step 1 agent to the use of thiazide diuretics, a recommendation that was validated by the results of clinical trials confirming the cardioprotective effect of β-blockers in patients following a myocardial infarction.[37] Concern about the adverse effects of diuretics and β-blockers on lipid levels and glucose tolerance led some authors to question whether the use of these medications should continue to be recommended as initial treatment.[38] An adequate assessment of patients' quality of life with the use of medications gained increased attention in the management of hypertension. In addition, the pharmaceutic industry aggressively markets new and more expensive medications to be used as initial therapy for hypertension based on a favorable adverse effect profile. The result has been that the prescribing habits of physicians in this country have evolved away from diuretics and β-blockers in favor of angiotensin-converting enzyme (ACE) inhibitors and calcium entry for the initial treatment of hypertension.

Recommendations for the stepped-care approach to hypertension underwent major changes in the 1988 JNC report.[1] First, nonpharmacologic therapy is recommended as step 1 for all patients because it will be an adjunct to medication if not effective alone. If the diastolic BP remains at 90 to 94 mm of mercury and the patient is otherwise at a low risk for cardiovascular disease, consideration should be given to not using any medications. Second, a menu of four medications is offered as step 2, which includes diuretics, β-blockers, ACE inhibitors, and calcium entry blockers. Clinicians are advised to select a low dose of medication from one class and evaluate its efficacy and adverse reactions over a one- to three-month period. A demographic profile and comorbid risk factors may help in selecting the type of medication. Third, if low doses of one type of medication are not effective, medication from a different step 2 category may be substituted for the first. Alternatively, low doses of a second medication may be added or the dose of the first medication used may be increased.[1]

Thiazide Diuretics

Thiazide diuretics have consistently been shown to lower the diastolic BP by 5 to 20 mm of mercury in most populations studied. Thiazides have the most extensive track record in the treatment of mild hypertension. The Medical Research Council trial found that β-blockers have similar efficacy in lowering diastolic BPs when compared with a diuretic.[16] None of the other candidates for initial pharmacologic therapy have been used in as many patients.

The VA Cooperative Study Group compared the use of hydrochlorothiazide with that of propranolol in 683 men of whom 58% were African American.[39] Results showed that the proportion of hypertensive African Americans with diastolic BPs of less than 90 mm of mercury was greater with hydrochlorothiazide use (71.3%) than with propranolol (53%). In addition, 10% of African Americans had an increase in their diastolic BPs on propranolol therapy, and, overall, African Americans required a lower dose of hydrochlorothiazide to achieve their goal diastolic BP. A one-year follow-up of 394 patients showed that the use of hydrochlorothiazide was more effective than that of propranolol in controlling the diastolic BP (65.5% versus 52.8%), but this was mostly a result of the observed racial differences in response.[39] Thus, hypertensive African Americans respond less well to treatment with β-blockers than do hypertensive whites, and a subset is at risk for having their blood pressure increase with treatment.

The age-adjusted prevalence of hypertension among Latinos in the US is no greater than that among white non-Latinos and may even be somewhat lower. Although less data are available for Asian Pacific Islander groups living in the US, only Filipinos have been shown to have a slightly higher prevalence of hypertension when compared with whites. There are no studies evaluating a differential response to antihypertensive medications in these ethnic groups.

Elderly persons with hypertension have an increase in peripheral resistance with a much lower adrenergic contribution to elevated diastolic BPs. The proportion of cases of hypertension involving low renin output in persons older than 60 years approaches 50% compared with an estimated 20% in younger populations. Thus, diuretics and calcium entry blockers may have a therapeutic advantage in elderly hypertensive patients. The experience from the Systolic Hypertension in the Elderly Program pilot study indicates that lower doses of diuretics—such as 12.5 mg of chlorthalidone per day—are effective and should be used initially.[40]

The efficacy and adverse effects of antihypertensive drug regimens in 690 men 60 years of age or older were recently reported by the VA Cooperative Study Group.[41] Low-dose regimens of hydrochlorothiazide (25 to 50 mg per day) lowered blood pressures by 18.3/9.5 mm of mercury compared with 20.4/9.6 mm of mercury with the use of high doses of hydrochlorothiazide (50 to 100 mg per day). The increase in serum cholesterol levels was lower with the low-dose regimen (0.16 versus 0.32 mmol per liter [6.2 versus 12.5 mg per dl]) and the decrease in serum potassium ion levels was less (−0.47 versus −0.63 mmol per liter).[41] There were no measurable adverse cognitive effects of lowering the blood pressure in these elderly men.[42]

Grimm and co-workers evaluated the effects in 57 men of a regimen of 100 mg per day of chlorthalidone and hydrochlorothiazide on lipid levels compared with placebo in a crossover design for 24 weeks.[43] Changes in lipid fractions in milligrams per deciliter are shown in Table 2. This study confirmed earlier observations that the administration of thiazide and related diuretics increased total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels in short-term follow-up. The observation that a low-fat diet blunted the deleterious changes in total and LDL-cholesterol levels is important to note.

Although the short-term effect of diuretic use on serum lipid levels is not disputed, there is little evidence that these changes are maintained for more than a year. In the VA study

comparing the use of hydrochlorothiazide with that of propranolol, cholesterol levels decreased by 0.20 mmol per liter (7.7 mg per dl) in the men treated with hydrochlorothiazide in doses as high as 200 mg per day.[39] Seven clinical trials or cohort studies have shown no changes or a decrease in serum cholesterol levels after long-term treatment.[44] Participants in MRFIT were evaluated at six years for lipid changes by category of intervention, with 1,947 receiving diuretics and diet and 2,537 on diet only.[19] Although the participants receiving diuretics had a lower decrease in total cholesterol levels and an increase in triglyceride levels, the decrease in LDL-cholesterol levels was similar. Similar effects were found for the use of β-blockers in smaller groups of patients. In HDFP participants, an overall decrease in total cholesterol levels was seen at two years in both the stepped-care and referred-care groups.[45] In the Medical Research Council trial, the use of bendroflumethiazide resulted in no change in total cholesterol levels for men and a slight reduction among women.[46]

The use of diuretics and β-blockers may provoke glucose intolerance in patients treated for hypertension, leading some authorities to recommend that persons with diabetes mellitus should not be treated with these medications. The hyperglycemic effect of thiazides is related to the level of hypokalemia, and prevention of the latter should minimize the development of, or exacerbation of, glucose intolerance.[47] The VA Cooperative Study Group has reported its experience with glucose intolerance in 340 men treated with hydrochlorothiazide and 343 men treated with propranolol.[48] At one year of follow-up, thiazide use on average had increased fasting glucose levels by 0.3 mmol per liter (6 mg per dl) and two-hour postprandial glucose levels by 1.8 mmol per liter (33 mg per dl). About 3% of patients treated with thiazides had a fasting glucose level of greater than 7.8 mmol per liter (140 mg per dl) at one year, but the average dose of hydrochlorothiazide used in this study was 93 mg per day. In the Medical Research Council trial, glucose intolerance caused more withdrawals from study medications in patients on diuretic therapy (9.38 per 1,000 patient years) than in those on propranolol therapy (3.65 per 1,000 patient years) or placebo (2.51 per 1,000 patient years).[46]

Thiazide diuretic use causes a dose-related decrease in total body and serum potassium levels with long-term therapy, but its effect on intracellular potassium may be minimal.[47] This kaliuretic effect is exacerbated by a high-sodium diet and, thus, can be prevented or minimized if patients cut sodium intake by about 50%. The average decrease in serum potassium levels with thiazide use is proportional to the daily dose, and given that the diastolic BP response to thiazides is relatively flat at doses greater than 50 mg a day, hypokalemia can usually be avoided by administering no more than 50 mg per day. Holland and colleagues and Hollifield and Slaton have reported that in about 10% of diuretic-treated patients in whom hypokalemia develops, there is potential for significant ventricular ectopic activity when the hydrochlorothiazide dose exceeds 50 mg per day.[49,50] The observed increased mortality in MRFIT participants was not correlated to changes in the serum potassium values.

TABLE 2.—*Lipid Changes at 24 Weeks in Men Treated With Diuretics**

Diuretic or Placebo	Lipid Changes, mg/dl†			
	Total Cholesterol	Low-Density Lipoprotein	High-Density Lipoprotein	Triglycerides
Placebo	1.8	1.5	3.2	−7.0
Hydrochlorothiazide, 100 mg/d	14.8	8.7	2.6	27.5
Chlorthalidone, 100 mg/d	18.8	14.0	2.3	23.1
Chlorthalidone plus diet	2.7	−2.1	2.1	17.7

*From Grimm et al.[43]

†Lipid changes are reported in conventional units. To convert to Système International units (millimoles per liter), multiply by 0.02586.

The benefit that thiazide diuretics may have in protecting elderly persons from hip fractures has been explored in two separate studies. Ray and associates in a case-control study from Saskatchewan showed that persons taking thiazide diuretics for more than two years had as much as a 50% decrease in the incidence of hip fractures.[51] More recently, LaCroix and co-workers prospectively studied the effects of thiazide diuretics on the incidence of hip fractures among 9,518 men and women 65 years of age or older living in three communities.[52] Over a four-year period, there were 242 hip fractures, and incidence rates were lower among the 24% to 30% of subjects on thiazide therapy at the start of the study. The multivariate adjusted relative risk of hip fracture was 0.68 (95% confidence interval [CI], 0.49 to 0.94), or a 32% reduction in risk.[52] These findings support an increased role for thiazide diuretics in treating elderly patients who have hypertension.

β-Adrenergic Blockers

There are 11 different types of β-adrenergic blocking agents available in the US, and all appear to be equally effective in the treatment of hypertension. Cardioselective β-blockers become less selective as dosage is increased but may offer advantages in patients with diabetes mellitus or chronic lung disease. Several β-blockers also have intrinsic sympathomimetic activity and result in less bradycardia.

In a recently reported case-control study, Psaty and colleagues evaluated the use of β-blockers for hypertension in patients in a health maintenance organization who had angina or myocardial infarction (n = 248 cases) and pharmacologically treated hypertension and were free of coronary artery disease (n = 737 controls).[53] Fewer cases than controls were taking β-blockers, and, after adjustment for confounders, the estimated relative risk for CAD for patients taking β-blockers was 0.62.[53] These data suggest that β-blockers may prevent first events of nonfatal myocardial infarction in patients with hypertension. Further analysis of these data has shown that subjects who recently stopped using β-blockers had a transient fourfold increase in the relative risk (RR) of CAD (RR = 4.5; 95% CI, 1.1 to 18.5).[54] The sudden withdrawal of β-blockers may precipitate angina and myocardial infarction in hypertensive patients without a history of CAD.

The decreased response of African Americans to propranolol therapy has been postulated to be due to their greater prevalence of low-renin-output hypertension. Clinical studies provide the strongest evidence for a differential response to antihypertensive treatment by race, but the presumed mechanisms are based on less convincing data. Overall, the available data indicate that African Americans are more responsive than whites to diuretic and calcium channel blocker therapy, especially when compared with β-blockers and ACE inhibitors.

Data on β-blockers indicate that although the total cholesterol level does not change substantially, high-density lipo-

protein-cholesterol levels decrease and LDL-cholesterol levels increase in short-term studies. β-Blockers with intrinsic sympathomimetic activity do not have lipid effects in short-term studies, but these medications also do not provide protection following a myocardial infarction. The long-term effects of β-blockers on lipid levels are not as evident, however. Berglund and Andersson examined six-year cholesterol and triglyceride levels in 49 patients treated with propranolol and found a slight reduction compared with baseline and one-year results.[55] The Medical Research Council trial did show a reduction in CAD mortality in nonsmoking propranolol-treated subjects, and the results of lipid changes did not indicate a canceling of the benefit provided by lower diastolic BPs.[16,46] Both men and women treated with propranolol in that study had a slight reduction in total cholesterol levels from baseline. The decrease was similar to that seen for women taking placebo and about a third that observed for men taking placebo. In the VA study, propranolol therapy resulted in a net increase of 0.5 mg per dl in total cholesterol levels (doses as high as 680 mg per day).[39]

There are no clear data to prove that an elevation of serum cholesterol levels by antihypertensive drugs is associated with an increased risk of CAD. The lack of a striking reduction in the incidence of CAD in the large hypertension trials has been blamed on the potential for atherogenicity that thiazide diuretics and β-blockers may have.[56] The most incriminating data on diuretics and propranolol indicate that they blunt the diet-induced decrease in cholesterol levels in persons with treated mild hypertension. The available longer follow-up studies on the lipid effects of diuretics and β-blockers do not support the idea that treatment with these drugs results in no net change in cardiovascular risk factors. Nevertheless, the initial choice of pharmacotherapy for a patient with hypertension and notably high serum cholesterol levels may be considered from alternative step 2 agents.

The use of β-blockers should be avoided if possible in diabetic patients requiring insulin because they mask most symptoms of hypoglycemia, but an additional direct effect on islet cells has also been found. In the VA Cooperative Study Group's comparison of thiazides and propranol, 1% of propranolol-treated patients had fasting glucose levels of greater than 7.8 mmol per liter (140 mg per dl) at the end of a year.[48] The average increase in fasting glucose and two-hour postprandial glucose levels was 0.3 and 1.0 mmol per liter (5.5 and 17.8 mg per dl), respectively. The hyperglycemic effect was dose-dependent, and the average dose of propranolol used in the study was 268 mg per day.

Nonselective β-blockers block the epinephrine-induced intracellular potassium shift that occurs with stress or during vigorous exercise. It has been speculated that this may contribute to the cardioprotective effects reported for these β-blockers.

Angiotensin-Converting Enzyme Inhibitors

The three ACE inhibitors available in the United States, captopril, enalapril, and lisinopril, are similar in effectiveness for the treatment of hypertension.[57] Hypertensive African Americans also respond less well to converting enzyme inhibitors, although the white-black difference can be substantially reduced by increasing the dose.[57] Racial differences in response to β-blockers and ACE inhibitors can be virtually abolished by combining treatment with a thiazide diuretic.

A comparative study of captopril, methyldopa, and propranolol, with hydrochlorothiazide added if needed, was completed by Croog and colleagues in 631 working white men.[58] Hydrochlorothiazide was added in 22% of subjects on a regimen of propranolol, 28% on a regimen of methyldopa, and 33% on a regimen of captopril. Although this study was primarily designed to evaluate the effect of medications on the quality of life, propranolol had a slight advantage in controlling the diastolic BP. Converting enzyme inhibitors have no adverse effects on lipid profiles or glucose tolerance in studies of as long as six months.[57]

Converting enzyme inhibitors may offer an advantage in treating hypertensive patients with diabetes. In addition to their blood pressure-reducing effects, ACE inhibitors are known to return the intraglomerular filtration pressure to normal, thereby decreasing the rate of nephron loss due to the consequences of glomerular hyperfiltration.[57] Marre and associates randomly assigned 20 normotensive diabetic patients with 0.03 to 0.3 grams (30 to 300 mg) of urinary protein per 24 hours to receive either enalapril or placebo for a year.[59] At the end of a year, none of the patients taking enalapril, but three taking placebo, had an increase in protein excretion to greater than 0.3 grams (300 mg) per 24 hours. In addition, five of the patients taking enalapril, but none taking placebo, had less than 0.03 grams (30 mg) of protein in 24-hour urine collections.[59] Once renal insufficiency becomes established, the potential benefit of ACE inhibitors on the renal function of diabetic patients is controversial. One report found that among 18 patients with hypertension, diabetes, and nephropathy, the addition of captopril helped decrease albuminuria and protect renal function when compared with those in 13 control patients.[60] In contrast, Valvo and co-workers found no significant effects on proteinuria and renal function after six months of captopril therapy in 12 patients with diabetic nephropathy.[61] Although hyperkalemia may be a greater risk when using ACE inhibitors in persons with diabetes, other advantages support their use as the initial drugs of choice in hypertensive persons with diabetes.

Converting enzyme inhibitor-induced cough is the major subjective adverse effect. A report from Boston found that 6 of 52 patients (12%) on a regimen of captopril and 23 of 93 patients (25%) on a regimen of enalapril complained of cough over a six-week period.[62] Gibson did a retrospective analysis of the records of 209 patients treated with enalapril and found that 22 (10.5%) had discontinued the drug because of cough.[63] An additional 29 (13.9%) reported cough but continued taking enalapril. It has been proposed that ACE inhibitor-induced cough may have its origins in the upper airways with possible mediation by afferent vagal C fibers.[27] Available data show that enalapril may be worse than captopril at inducing cough.

Schoenberger and colleagues reported that a postmarketing survey of 30,515 patients receiving monotherapy with captopril showed that only 4.9% reported an adverse event requiring the discontinuation of therapy.[64] Headaches (1.8%) and dizziness (1.6%) were the most common reported adverse effects, with cough reported in only 0.8% of patients.[64] Self-reported quality of life measures improved with captopril therapy.

Williams and Hollenberg have noted that there is a distinct subset of patients with essential hypertension who they label nonmodulators.[65] This subset is based on the fact that

sodium intake does not modify renovascular and adrenal responses to angiotensin II. These patients have a hypertensive response to a salt load—that is, salt sensitivity—but renal blood flow does not increase, and, thus, there is a reduced ability to excrete a salt load. Converting enzyme inhibitors may be more effective in this subset of patients because they specifically correct the underlying pathophysiologic derangement. The practical implications of this observation in choosing an antihypertensive medication are not clear.

Calcium Entry Blockers

Calcium entry blockers are effective first-line drugs in treating mild hypertension. Although verapamil, diltiazem, nifedipine, and nicardipine are equally effective in treating hypertension, they have differential effects on the cardiac conduction and the degree of peripheral vasodilator function.[66] Because of these differences, adverse effect profiles vary. Although calcium entry blockers—verapamil more than nifedipine or nicardipine, but not diltiazem—may exacerbate glucose intolerance by reducing insulin release, the clinical importance of these effects is questionable. There are no reported adverse effects on lipids.

With the availability of sustained-release formulations of verapamil, diltiazem, and nifedipine, there is no reason to administer the calcium entry blockers other than once or twice a day when treating hypertension. Sustained-release formulations of calcium entry blockers eliminate the peaks and troughs seen with the immediate-release formulations. Consequently, many of the adverse effects noted (especially with nifedipine) are decreased considerably or eliminated.

All calcium entry blockers should be administered with caution in patients with heart failure as they have negative inotropic effects.[66] Clinical trials have not shown a cardioprotective benefit of calcium entry blockers following myocardial infarction, except in patients with normal left ventricular function who tend to do well regardless of drug therapy.[67] Two recent reports indicate that calcium entry blockers may have an important role in preventing heart disease related to hypertension. Schulman and associates compared the effects of verapamil and atenolol therapy on left ventricular mass in 42 patients older than 60 years.[68] They found that a reduction of left ventricular mass occurred more often with the use of verapamil than with atenolol and that systolic function was not impaired.[68] In a randomized, placebo-controlled trial, Lichtlen and co-workers in West Germany found that nifedipine treatment in patients with mild coronary artery lesions resulted in a 28% reduction in the number of new lesions seen on arteriograms.[69] If other studies using clinical outcomes confirm these findings, calcium entry blockers may become increasingly attractive medications for treating hypertension.

Calcium entry blockers as single agents work equally well in African Americans and whites with hypertension.[66] Verapamil has been compared with propranolol and analyzed as to racial group response in a study of 118 patients. After four weeks of therapy, results showed that verapamil decreased blood pressures equally in whites (−19/−16.7 mm of mercury) and blacks (−16.9/−12.8 mm of mercury) compared with propranolol, which was more effective in whites (−12.7/−12.3 mm of mercury) than in blacks (−8.1/−8.6 mm of mercury).[70] Kaplan disputes the observation that calcium entry blockers are more effective in older persons.[66] The hypotensive effect of adding a thiazide-type diuretic to a calcium entry blocker is additive but not synergistic as with a β-blocker or a converting enzyme inhibitor.

Effect on Quality of Life: Do No Harm

The effect that the diagnosis and treatment of hypertension has on a person's quality of life is a variable that had received relatively little attention until this past decade. The presence of elevated diastolic BPs in 20% of whites and 30% of African Americans in the US means that millions of persons without any symptoms are given a diagnosis of hypertension. The labeling of persons with a diagnosis of hypertension leads to increased absenteeism from work and an increased number of physician visits in the ensuing year.[71-73] Untreated mild hypertension, however, may lead to pathologic changes in small arterioles that may result in impotence or decreased cognitive function.

Jachuck and colleagues reported an interesting observation in 41 women and 34 men treated for hypertension in a general practice in Great Britain.[74] They questioned the patients, close relatives or spouses, and the patients' physicians regarding overall assessment after a year of treatment. Physicians perceived all patients as having an improved quality of life, 48% of the patients themselves agreed, but only one relative found improvement. Almost half of all patients found no change in their quality of life, but 99% of all relatives questioned thought that the patient had gotten worse since starting treatment for hypertension.[74] They observed symptoms of decreased memory (33%), irritability (45%), depression (46%), more hypochondria (55%), and decreased sexual interest (64% of spouses). The 75 patients studied were treated with diuretics (41), β-blockers (36), methyldopa (18), and other drugs (6).[74]

Most clinical trials evaluating pharmacotherapy for hypertension have published self-reported adverse effects. Studies have shown that centrally acting drugs such as methyldopa cause sedation, fatigue, depression, and decreased memory.[75] The lipophilic β-blockers (propranolol more than acebutolol more than timolol more than metoprolol more than pindolol) should be expected to cause more central nervous system symptoms than the hydrophilic β-blockers (atenolol, nadolol) because they penetrate the blood-brain barrier more effectively. The data documenting the adverse effects of β-blockers on cognitive function are generally insufficient, however.[76] Thus, it is difficult to conclude anything about the importance of lipophilicity in causing adverse effects. A study comparing atenolol and propranolol found no significant differences in cognitive function.[77] The use of ACE inhibitors, calcium entry blockers, and α_1-blockers has not been associated with significant effects on cognitive or emotional function.

The Medical Research Council trial reported that 22% of men on diuretic therapy, 13% on propranolol therapy, and 10% taking a placebo had impotence.[46] Croog and associates reported that propranolol had a substantial adverse effect on sexual function when compared with captopril.[78] The absence of incriminating data and the general clinical impression indicate that ACE inhibitors, calcium channel blockers, and α_1-antagonists cause the least perturbation of sexual function.

Croog and co-workers published a prospective study evaluating the effects on quality of life of antihypertensive pharmacotherapy.[58] Regimens of captopril (n = 213), propranolol (n = 212), and methyldopa (n = 201) were com-

pared in 626 working men, aged 21 to 65 years, with diastolic BPs between 90 and 109 mm of mercury over a six-month period of study. Patients were randomly assigned to one of three treatments, followed up for blood pressure measurements, and several blinded measures of quality of life were used. Fewer patients withdrew from the drug when taking captopril (8%) compared with methyldopa (20%) or propranolol (13%). No differences were noted in measures of sleep dysfunction, visual memory, or social participation. Captopril therapy resulted in a greater sense of general well-being, fewer total side effects, and better scores for work performance, visual-motor function, and life satisfaction when compared with methyldopa therapy. The use of propranolol also led to better work performance than did methyldopa but caused more total side effects and sexual dysfunction than using captopril. Patients taking hydrochlorothiazide (step 2 for each treatment) did worse as a group.[58]

This study has had an important influence on pharmacotherapy for hypertension. First, it has reminded physicians that for most patients, hypertension is an asymptomatic risk factor and not a disease. Most patients with diastolic BPs of 90 to 94 mm of mercury will do well regardless of therapy. Counseling on cigarette smoking, diet, and other behavioral factors would be a more efficient use of effort and time. If the treatment of mild hypertension is preventive medicine, then the benefits and risks of treating a patient with a medication that may cause significant objective symptoms should be carefully evaluated. Second, the study confirmed the well-known frequent side effects that occur with the use of methyldopa, and its continued use as an antihypertensive should be questioned. Third, the study thrust captopril and the other ACE inhibitors into the forefront of antihypertensive pharmacotherapy. The relatively good adverse effect profile of ACE inhibitors is one of their most attractive features. Finally, more clinical studies on the treatment of mild hypertension should be evaluating sexual function, depressive symptoms, cognitive function, and other subjective symptoms with quantitative scales used in the behavioral sciences.

Cost of Therapy: How Much Is Preventive Medicine Worth?

There is increasing political and societal pressure to rein in the high cost of medical care. The management of hypertension cannot escape the controversy given the expense of evaluations, follow-up, and pharmacotherapy. The application of more expensive technology in the routine workup for hypertension includes the use of an echocardiogram to determine left ventricular mass and provide a better prognostic indicator, a 24-hour ambulatory recording to rule out white coat hypertension, and an exercise treadmill test to identify an exaggerated hypertensive response to exercise. These maneuvers would add at least $600 (without considering follow-up studies) to each evaluation. On the other hand, these tests may help identify subsets of patients who would not benefit from lifelong pharmacotherapy and those for whom more intensive therapy would be beneficial.

The cost of daily drug therapy need not be a predominant determinant of choosing a regimen. Some patients cannot afford expensive medications, however, and will not always volunteer this information to their physicians; thus, compliance with a regimen may be related in part to the cost of medications.[79] In 1987 Moser compared the estimated cost per year of different medications as follows[80]: $30 to $35 for generic diuretics, $50 to $75 for nongeneric diuretics, $100 to $125 for combinations that include a potassium-sparing diuretic, $150 to $175 for generic propranolol, $200 to $225 for other β-blockers, and $400 to $700 for ACE inhibitors and calcium entry blockers.

Edelson and colleagues in Boston have recently reported a long-term cost-effectiveness analysis of several initial monotherapies for mild to moderate hypertension using a computer simulation of overall mortality as well as mortality, morbidity, and cost of coronary artery disease in the US population.[81] For 20 years of simulated therapy, the cost per year of life saved was projected to be $10,900 for propranolol, $16,400 for hydrochlorothiazide, $31,600 for nifedipine, $61,900 for prazosin, and $72,100 for captopril.[81] Lowering the diastolic BP by 1 mm of mercury was equivalent to lowering the cholesterol level by 6%. Although these projections require multiple estimates that can be debated, propranolol therapy appears to be the preferred initial option.

Conclusions

Step 1 therapy for most patients with mild hypertension (diastolic BP, 90 to 104 mm of mercury) should be nonpharmacologic. Dietary changes that help reduce weight, decrease alcohol ingestion, and modify the amount of sodium chloride, potassium, and calcium in the diet are the principal ways of lowering the blood pressure without drugs. Aerobic exercise and relaxation therapy may also contribute to decreasing diastolic BPs.

Nonpharmacologic treatment should be tried a minimum of three to six months in most patients before initiating medication therapy. In persons with low cardiovascular risk profiles, the diastolic BP threshold for drug therapy should be raised to 100 mm of mercury and nonpharmacologic treatment used at least a year. Patients with comorbid conditions mandating drug therapy from the beginning should also be advised regarding nonpharmacologic approaches.

In considering medication alternatives, the following factors should be noted: efficacy, comorbid conditions, quality of life, metabolic side effects, demographic profile, and cost.

Step 2 therapy for mild hypertension can be selected from one of four classes of medications: thiazide diuretics in low doses (25 mg) for African Americans, the elderly, smokers, and persons with a normal ECG; β-blockers for whites, nonsmokers, younger patients, and those with known coronary artery disease; ACE inhibitors for whites, younger patients, those with a total cholesterol level of greater than 6.21 mmol per liter (240 mg per dl), and persons with diabetes; and calcium entry blockers for the elderly, those with CAD present, and hypercholesterolemia. The choice of a specific medication should depend on the individual characteristics of a patient. From a public policy perspective, generic diuretics are preferred. β-Blockers, however, prevent CAD mortality in nonsmokers and should be the first choice in these patients. The ACE inhibitors offer the advantage of a low side-effect profile, may prevent nephropathy in diabetic patients, and will be more attractive as their cost decreases.

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SYNCHRONICITY

You've experienced it—
something you barely knew about
shows up everywhere now

that it has happened to you.
Mid-sitcom plot, a spot
for the American Cancer Society;

Between single and double Jeopardy,
news about the latest carcinogen.
I don't look at my mother's face

when this happens, but wonder
if she thinks about cancer
or about me thinking about it.

Now that I think about it,
it is no more about me
than other pairings of Xs and Ys.

She has her own anguish—apart from me.
She takes it home with her.
It rides along to the supermarket,

sits beside her at bridge.
She carries it to church
where it becomes a prayer.

It does something I never see
to her face. This face
she turns to her husband

in the hospital corridor,
and would be the same
face were it my sister

or one of my brothers
lying here instead of me.
My mother's child has cancer.

LIZ PARKER©
Cypress, California

MY FATHER'S HANDS

My mother takes me to the hospital.
She sees me into, then out
of surgery, helps me through
not the first or last, but current pain.
She cools my face with damp towels
and badgers the nurse for morphine.
At my house, my father waits
the only way he knows. He builds
a shelf beside my bed, makes
leaves for my dining room table.

A week later, we eat breakfast
on the patio. I am not dying
today. We talk of practicalities,
the logistics of getting me
to and from treatment. I worry
about the bills piling up
after only a month. My father says,
"We'll help you. You must know
that if we couldn't, we'd be desolate."
I think, "desolate?" And yet somehow
it is the right word—a cross
between desperate and inconsolable.

My mother changes my dressings,
brings me shaved ice
when nothing else stays down.
My father builds for me a fireplace.
I will have a hearth, and a mantle
from oak already older than I.
From my bedroom, I hear the tap tap
of trowel handle as he levels each brick.
I picture his hands and their rhythm
with brick and mortar. Scoop, fling,
tap, tap, scrape around, fling. Lulled
by the certain rhythm of my father
laying brick, I sleep. Scoop, fling,
tap, tap, scrape around, fling.

My father heals the only way he knows.
He builds things to last me a lifetime.

LIZ PARKER©
Cypress, California

Epitomes

Important Advances in Clinical Medicine

Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in pathology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Tumor Necrosis Factor in Human Disease

THE ACTIVE FORM of human tumor necrosis factor α (TNF; cachectin) is a 157-residue (17-kilodalton) polypeptide cytokine. Its gene is located in the short arm of chromosome 6, near the gene of lymphotoxin (TNFβ), another cytokine that shares some of its biologic activities. The best known sources of TNF are monocytes and macrophages, which secrete copious amounts of this protein on stimulation by endotoxin (lipopolysaccharide). In addition, T lymphocytes (CD4 and CD8), natural killer cells, Kupffer cells, microglia, and astrocytes appear to produce TNF. This cytokine, described in 1975, has been sequenced, cloned, and produced by recombinant techniques in humans in 1985 and in mice in 1986.

Tumor necrosis factor can be measured by biologic assays, such as using its property to lyse fibroblasts of the L929 or WEHI 164/13 lines, or by immunologic assays using monoclonal antibodies of various specificities. The latter include enzyme-linked immunoassays (ELISA) and immunoradiometric assays (IRMA), which currently allow the detection of TNF in the range of 1 to 10 pg per ml. This high level of sensitivity will be useful in establishing the normal concentrations in various tissues that are probably of great physiologic importance. Receptors for TNF have been found in normal tissues including lungs, liver, kidneys, intestine, and skeletal muscle. Endothelial cells are among those with high-affinity receptors. Injected TNF has a short half-life in plasma of 6 to 7 minutes. Normal plasma or serum levels are below 15 pg per ml.

The physiologic roles of TNF are the least known of its effects, partly because of the insensitivity of previous methods. Nevertheless, it appears that TNF is important at least in the inflammatory response and in tissue remodeling. In inflammation, TNF increases the chemotaxis of neutrophils and macrophages and the adhesion of leukocytes to endothelium, partly by increasing the expression of adhesion molecules such as intercellular-leukocyte and endothelial-leukocyte adhesion molecules (ICAM and ELAM). Tumor necrosis factor is one of the cytokines that induce expression of the histocompatibility antigens, such as class I major histocompatibility complex in endothelial cells. It is likely that many of the TNF effects are not direct but are mediated through substances known to be stimulated by TNF. These include other cytokines (interleukin 1 and 6, granulocyte-macrophage colony-stimulating factor, platelet-derived growth factor, and transforming growth factor-β), prostaglandins, and hormones (catecholamines, glucagon, and the like). In its tissue remodeling role, TNF promotes the proliferation of fibroblasts and perhaps smooth muscle. In endothelial cells it induces the expression of tissue factor and of the inhibitor of tissue plasminogen activator, as well as the synthesis of collagenases, proteases, and prostaglandins. It is also directly toxic to endothelial cells. It has been proposed that TNF induces wound healing, but there are conflicting data about its role in angiogenesis.

The pathologic effects of TNF are better known. These include cachexia, septic shock, severe inflammatory reactions, and intravascular coagulation. Prolonged exposure to TNF alters several metabolic enzymes. In particular, it suppresses lipoprotein lipase and inhibits other lipid enzymes. The result is lipolysis, triglyceridemia, and glycogenolysis. In experiments, animals with long-term exposure to TNF become anorectic and depleted of protein and lipids. It is likely that anorexia and consequent cachexia in humans result from increased levels of TNF in various pathologic conditions including malignant neoplasms.

The rapid intravenous administration of lipopolysaccharide—4 ng per kilogram of *Escherichia coli* endotoxin—in humans has caused high peaks (~ 240 pg per ml) of plasma TNF 90 to 180 minutes later, coinciding with fever, chills, myalgia, rigor, headache, nausea, and tachycardia. There was a simultaneous elevation of blood adrenocorticotropin, cortisol, and catecholamines. Leukocytosis occurred four hours later, when the plasma TNF level was almost undetectable. The symptoms, but not the rise in TNF levels, were prevented by administering a cyclooxygenase inhibitor. Similar symptoms, plus hypotension, have occurred in volunteers receiving a bolus of recombinant TNF.

Larger doses of TNF in other species cause irreversible shock identical to the septic shock syndrome. That TNF is often responsible for septic shock is supported by a recent trial of anti-TNF monoclonal antibody. In 14 patients with septic shock, administering the antibody raised the blood pressure and prolonged survival. The experimental local effects of high tissue levels of TNF include hemorrhage, tissue

necrosis, and abscesses. The systemic effects include disseminated intravascular coagulation. Increased levels of TNF in humans would likely result in similar alterations.

The importance of TNF in human diseases was first reported in patients with gram-negative sepsis (purpura fulminans of meningococcemia). Also, it has a pathogenetic role in cerebral malaria, both human and experimentally induced. In both of these life-threatening conditions, elevated blood TNF levels on admission have correlated with an increased incidence of death or sequelae. Based on experimental data, the use of anti-TNF antibodies is promising as a therapeutic tool. Clinical trials of monoclonal antibody are underway in patients with gram-negative septic shock, cerebral malaria, and the OKT3-induced syndrome (in the context of transplantation).

Other conditions associated with alterations of TNF in humans include rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitis, cystic fibrosis, graft-versus-host disease, sarcoidosis, some parasitic infections (aside from malaria), septic arthritis, leprosy, and the acquired immunodeficiency syndrome. Patients with chronic heart disease have high serum levels of TNF, especially if they are cachectic. Such elevations in cachectic patients may be associated with activation of the renin-angiotensin system. In some conditions where blood TNF alterations are not detectable, dramatic changes may be found in other body fluids, such as in bronchial aspirates of patients with the adult respiratory distress syndrome.

It appears that some neoplasms, including a human breast carcinoma and a mouse fibrosarcoma, secrete TNF in vitro. There is even a transplantable mouse tumor line genetically altered to continuously secrete human TNF. Thus, the possibility of using levels of blood TNF as markers of neoplastic activity has been raised. Some investigators have found TNF immunoreactivity in the serum of 50% of patients with ovarian, breast, and colon carcinoma, lymphomas, and myeloma; in 18% of patients in complete remission; and in 3% of normal subjects. Other investigators have not detected TNF in cancer patients. Discrepant results of some TNF assays could be explained by the presence of TNF inhibitors, which would inhibit bioactivity but not immunoreactivity.

Although the name "tumor necrosis factor" was derived from the observation that it produced lysis of a murine tumor, subsequent research on its putative antineoplastic effects has been generally disappointing, especially for human tumors. It is cytotoxic for some animal (such as L929 fibroblasts) and human tumor cell lines and does cause necrosis of some experimental neoplasms, but it seems to be ineffective in vivo against a good many human tumors, and toxicity is often reached before tumoricidal effect. Nevertheless, clinical trials with recombinant TNF are in progress. It is possible that the addition of other cytokines, or conventional chemotherapy, radiotherapy, or hyperthermia may potentiate the antineoplastic effects of tolerable doses of TNF.

LUIS F. FAJARDO, MD
Palo Alto, California

GEORGES E. GRAU, MD
Geneva, Switzerland

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Pathologic Mechanism of Pulmonary Graft Rejection

SINGLE-LUNG, DOUBLE-LUNG, and combined heart-lung transplantation have become life-saving therapeutic procedures for patients with end-stage pulmonary diseases. Graft rejection and infections compose the major posttransplant complications and can be diagnosed by fiberoptic bronchoscopy with transbronchial biopsy.

The precise incidence of acute rejection in lung allograft recipients is unknown, but it has been estimated to be about 50% during the first two to three weeks after the procedure. Mild acute rejection is characterized by the development of interstitial edema and mild perivascular infiltrates by transformed lymphocytes, small lymphoid cells and eosinophils, endothelial cell swelling with occasional infiltration by lymphocytes (endothelialitis), and bronchial infiltrates by lymphoid cells and eosinophils or acute vasculitis, or both. These histopathologic features are usually patchy, and their diagnosis requires the examination of several histologic slides from each specimen.

Moderate rejection is characterized by prominent perivascular and bronchial lymphoid infiltrates with extension of the inflammatory cells into the alveolar septa. In severe rejection, the lung undergoes hemorrhage and infarction with thrombosis of arteries and veins and vasculitis with fibrinoid necrosis.

The diagnosis of chronic rejection in heart-lung transplant recipients remains controversial, but progressive pulmonary dysfunction due to bronchiolar and vascular complications has been described in about half of the long-term survivors. Obliterative bronchiolitis is the most important chronic complication in these patients. It can appear as early as 2 months after transplantation but usually results in respiratory symptoms at 11 to 12 months after the operation. In the early stages of obliterative bronchiolitis, the involved airways show ulceration and infiltration of their wall by inflammatory cells, followed by reepithelialization and intraluminal growth of granulation tissue with fibroblasts resulting in a scar that obliterates the airway lumen.

Vascular complications include the development of an unusual form of accelerated atherosclerosis with concentric proliferation of myofibroblasts in the intima of pulmonary veins and arteries resulting in intimal sclerotic thickening.

ALBERTO MARCHEVSKY, MD
Los Angeles, California

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Human Immunodeficiency Virus-Associated Nephropathy

THE KIDNEYS HAVE EMERGED as intriguing organs of involvement in patients infected with the human immunodeficiency virus (HIV). In addition to infections and neoplasms, HIV-associated nephropathy has become an important manifestation of HIV infection. This disorder typically presents with heavy proteinuria and progressive renal insufficiency without hypertension. The kidneys are large at the beginning and usually remain so during the course of the disease. On microscopic examination there are consistent abnormalities in the glomeruli, tubules, and interstitium. The glomerular lesion is of focal and segmental glomerulosclerosis, often in an early stage of evolution. Clusters of visceral epithelial cells are enlarged and coarsely vacuolated, and capillary walls are partially collapsed. Capillary lumina may contain foam cells. There is degeneration and necrosis of tubular epithelium. Many tubules are microcystically dilated and filled with plasma protein-containing casts; Bowman's spaces are dilated and contain the same material. The interstitium is edematous and is infiltrated by scattered lymphocytes. At the ultrastructural level, there is effacement of the foot processes of visceral epithelial cells. Tubuloreticular structures are widespread in all vascular endothelium and occasionally in mesangial cells and epithelial cells. Furthermore, nuclear bodies and granular and granulofibrillar transformation of nuclei are also found. Immunofluorescence reveals granular immunoglobulin M and complement deposits mainly in the abnormal glomerular segments.

Because the ultrastructural cellular abnormalities are often associated with viral infections, one of the major considerations for the pathogenesis of HIV-associated nephropathy is of direct viral infection of renal epithelium. Using a complementary DNA probe, we documented HIV genome in renal glomerular and tubular epithelium, suggesting that HIV may be important in the initiation or progression of this disorder. This observation, however, leads to many unanswered questions, among which are, How does virus enter the CD4-negative renal epithelium? Are other factors, including infection with other viruses and hereditary considerations, also necessary?

A number of clinical features are worth noting. More than 90% of reported patients are African American; about 50% are intravenous drug abusers. Renal disease may antedate the development of other features of HIV infection, such as acquired immunodeficiency syndrome (AIDS)-related complex and AIDS. Indeed, about a third of the currently diagnosed cases of HIV-associated nephropathy in the United States are in patients who are HIV carriers. It is not unusual for a pathologist to suggest that the HIV-antibody status of a patient be determined based on a characteristic and diagnostic constellation of structural abnormalities in a renal biopsy specimen obtained to assess heavy proteinuria and azotemia. Renal function rapidly deteriorates; in most patients, end-stage renal failure develops within 6 to 12 months.

ARTHUR H. COHEN, MD
Torrance, California

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Fine-Needle Aspiration Biopsy in the Diagnosis of Pediatric Tumors

DIAGNOSING TUMORS in children presents a special set of circumstances in which the desire for diagnostic techniques of low morbidity and good patient acceptance must be balanced with requirements for high diagnostic accuracy. While fine-needle aspiration biopsy (FNAB) is a cost-effective technique with good patient acceptance, it has received limited acceptance among pediatricians as an initial diagnostic tool. The relative rarity and small cell nature of many pediatric neoplasms have caused pathologists to be uneasy with the cytologic diagnosis of these tumors. In addition, many palpable nodules in children represent reactive lymphoid proliferations difficult to separate from lymphoma or leukemia on purely morphologic grounds. Recent advances in the areas of immunocytochemistry, molecular biology, and DNA probe technology have improved the diagnostic accuracy of FNAB for the evaluation of these proliferations.

Diagnosing small round cell tumors of children by FNAB offers some advantages over diagnosis by open biopsy in that surgical excision may be delayed until after chemotherapy has reduced the tumor size. The limited size of the specimen obtained by FNAB, however, may deprive a treating oncologist of valuable information relating to histologic grade, tumor karyotype, and oncogene amplification status. Advances in tissue culture, oncogene identification, and immunocytochemical techniques have allowed the identification of chromosomal abnormalities, differentiation markers, and oncogene amplification in specimens obtained by aspiration. While FNAB is currently most useful in the diagnosis of recurrent or high-stage disease, future advances in molecular biology may allow FNAB to supply prognostic and therapeutic information now available only by open biopsy.

Fine-needle aspiration represents a simple method for separating patients with clinically suspicious adenopathy into surgical and nonsurgical candidates. The combination of morphologic analysis with immunocytochemical documentation of light-chain clonality appears highly accurate for distinguishing benign adenopathy from lymphomas. Patients with cytologically and immunohistochemically benign adenopathy may be observed attentively and patients with morphologically suspicious disease should undergo open biopsy. Following this scheme, the number of biopsies done for adenopathy can be reduced.

Fine-needle aspiration biopsy can yield valuable diagnostic information in various head and neck lesions. It has been shown to be an accurate method for evaluating thyroid nodules and can identify a variety of embryologic rests within the head and neck. The ease of FNAB coupled with its high diagnostic accuracy makes it a desirable method for diagnosing lesions arising in children.

LESTER J. LAYFIELD, MD
Los Angeles, California

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Molecular Mechanisms of Heart Muscle Disease

SUBCELLULAR MECHANISMS of dilated heart muscle disease (congestive cardiomyopathy) are poorly understood. With the development of techniques of molecular biology, some causal events in a specific form of congestive cardiomyopathy, the form induced by the anthracycline doxorubicin (Adriamycin) hydrochloride, have recently been elucidated. Postulated mechanisms of doxorubicin congestive cardiomyopathy include DNA intercalation, free-radical injury, lipid peroxidation, and mitochondrial damage. It has been shown that a relatively specific effect of doxorubicin use is selective changes in the expression of cardiac α-actin (α_c-actin) polypeptide and messenger RNA in vitro and by analogous studies in vivo. This selective defect in the expression of a critical sarcomeric protein may ultimately relate to the defective contractility in doxorubicin congestive cardiomyopathy.

Data show that doxorubicin has a relatively selective effect on the steady-state expression of α_c-actin mRNA compared with nonsarcomeric β-actin or glyceraldehyde-3-phosphate dehydrogenase mRNAs in the rat heart in vivo in both a dose-related and a temporal way in which the nadir acute doxorubicin effect occurred three days after therapy. It has been known for years that doxorubicin congestive cardiomyopathy is related to cumulative doxorubicin therapy. Many antineoplastic chemotherapy regimens use sequential doxorubicin administration, which may empirically correlate with recent in vivo- and in vitro-derived scientific data.

The defect in the expression of α_c-actin mRNA induced experimentally by doxorubicin may relate to cumulative toxic effects. We have initiated an experimental model for recovery of the heart from doxorubicin's cardiotoxic effects. In this model, cardioprotective agents are used to prevent doxorubicin cardiotoxicity. Preliminary data suggest that the effect of the drug on α_c-actin mRNA expression cannot be ablated by administering some cardioprotectant agents such as ICRF 187.

Molecular biologic methods have been applied more recently to the emerging problem of congestive cardiomyopathy in the acquired immunodeficiency syndrome (AIDS) to explore its subcellular mechanisms. Preliminary data suggest that zidovudine (AZT), the widely used antiretroviral drug, has an associated cardiotoxicity in rats that is manifested ultrastructurally by mitochondrial disarray in cardiac myocytes. The doses used in the experimental system were relatively high compared with those used in AIDS therapy at present. Future work will explore the molecular mechanisms of AZT cardiotoxicity by attempting to localize the molecular targets that may correlate with the observed cardiac ultrastructural changes induced by AZT by using methods adapted from doxorubicin-induced congestive cardiomyopathy models.

The pathogenetic mechanism of drug-induced congestive cardiomyopathy may not directly relate to a depressed expression of α_c-actin mRNA in the heart. Nonetheless, it is intriguing to find that depressed α_c-actin mRNA expression in the myocardium appears to relate pharmacologically to doxorubicin administration. Future studies may link doxorubicin-induced congestive cardiomyopathy mechanistically with defects in the expression of sarcomeric proteins and mRNAs, particularly α_c-actin. Studies of models of the disorder provide a better understanding of the molecular mechanisms that are involved in the regulation of myocardial actin homeostasis in health and potential derangements in heart muscle disease.

WILLIAM LEWIS, MD
THOMAS PAPOIAN
Los Angeles, California

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Hepatitis C Test

NON-A, NON-B HEPATITIS, defined as hepatitis resulting from infection with agents other than the hepatitis A or B viruses, is the most frequent transfusion-associated infection in the United States and a major cause of transfusion-related morbidity and mortality. Studies in the late 1970s showed that non-A, non-B hepatitis developed in as many as 10% of transfusion recipients. Although the acute infection is usually asymptomatic, chronic liver disease will develop in 50% of infected patients, and in 20% of these, cirrhosis may develop. In the absence of a specific test for the causative agent of non-A, non-B hepatitis, blood banks in the mid-1980s began screening donors for elevated levels of alanine aminotransferase (formerly glutamic-pyruvic transaminase) and antibody to the hepatitis B core protein. These tests were predicted to identify 30% to 40% of infectious blood donors.

Transmissivity studies in animals indicated that the major causative agent of non-A, non-B hepatitis was a small RNA virus, although many attempts to isolate this agent were unsuccessful. Recently investigators at the Chiron Corporation and the Centers for Disease Control took a novel approach and synthesized components of this virus using recombinant DNA technology. The investigators isolated nucleic acid from the plasma of a chimpanzee with non-A, non-B hepatitis and inserted pieces of this material into bacteria. Of 1 million recombinant bacterial colonies screened, 1 expressed a protein recognized by antibodies from patients with non-A, non-B hepatitis. The genetic insert in this colony was identified, and a larger genetic clone containing this sequence was then inserted into yeast. The recombinant protein produced by this yeast, called the C100-3 protein, is the basis for the hepatitis C virus (HCV) screening test licensed by the Food and Drug Administration (FDA) on May 2, 1990.

The HCV screening test detects antibodies that bind to the C100-3 protein. A large majority of patients with chronic non-A, non-B hepatitis, both transfusion-associated and nontransfusion-associated, have antibodies to this protein. The

test has limited value, however, in the diagnosis of acute hepatitis. Antibodies to the C100-3 protein do not appear until an average of 22 weeks from the time of infection and may not appear for a year or longer. Some patients may lose antibody to this protein at different phases of their liver disease.

Blood banks instituted the HCV screening test as soon as it was licensed by the FDA. Approximately 0.4% to 1.5% of volunteer blood donors have a reaction with this test. It is estimated that the use of this screening test will further decrease the rate of transfusion-transmitted non-A, non-B hepatitis by at least 50%.

False-positive reactions on the HCV screening test occur. Research confirmation tests, available from the manufacturers of the screening tests, indicate that as many as 40% to 60% of the reactions in blood donors are false-positive—that is, unrelated to hepatitis C. Among populations at high risk for non-A, non-B hepatitis, however, such as persons with hemophilia and intravenous drug users, almost all reactions are confirmed. Preliminary data suggest that the results of these confirmation tests correlate with infectivity.

Preliminary epidemiologic studies using the HCV screening test indicate that there is a low risk of nonparenteral viral transmission but that there may be an association of hepatitis C with cirrhosis, hepatocellular carcinoma, and possibly "idiopathic" liver diseases. These issues will have to be examined more closely in conjunction with the use of confirmatory tests.

Investigators have now successfully sequenced the entire genome of hepatitis C, which they have established to be a single-stranded RNA virus with a structure similar to flaviviruses. Other regions of the viral genome are now being investigated in search of other immunogenic viral components.

It is remarkable that this infectious agent that has so long eluded isolation or even visualization has finally been characterized. Although there are other agents which can cause non-A, non-B hepatitis, this recent accomplishment will go a long way toward improving the safety of the blood supply and our understanding of the epidemiology and natural history of the major form of non-A, non-B hepatitis.

SUSAN GALEL, MD
EDGAR ENGLEMAN, MD
Palo Alto, California

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Epstein-Barr Virus in Hodgkin's Disease

On the basis of epidemiologic and serologic studies, Epstein-Barr virus has long been suspected to be implicated in the pathogenesis of Hodgkin's disease. Recently researchers used molecular hybridization techniques and in situ hybridization to demonstrate the presence of Epstein-Barr viral DNA in about 20% of tissues involved by Hodgkin's disease. Other investigators have used Southern blot testing to show Epstein-Barr viral DNA in between 16% and 29% of patients with Hodgkin's disease. Analyses of cases of Hodgkin's disease by dot blotting and polymerase chain reactions have generally produced similar results, except for a preliminary study in which about 60% of patients with lymphocyte-predominant Hodgkin's disease were found to have cells whose DNA contained Epstein-Barr virus-related sequences. In that study, DNA from formalin-fixed, paraffin-embedded tissue was analyzed after 40 cycles of the polymerase chain reaction and compared with control specimens.

Messenger RNA coding for interleukin 5 has recently been detected in Reed-Sternberg cells and variants in patients with Hodgkin's disease. In view of a report that Epstein-Barr virus-infected cells synthesize interleukin 5, it is reasonable to speculate that the expression of the interleukin 5 gene in Reed-Sternberg cells may be related to infection by Epstein-Barr virus. The presence of interleukin 5 in Epstein-Barr virus-infected cells of Hodgkin's disease could explain the frequent presence of eosinophilia and hyperglobulinemia in patients with Hodgkin's disease. As techniques to detect the Epstein-Barr virus become more refined, it is likely that additional persons with Hodgkin's disease will be shown to be infected with this virus. Such a finding will have important implications for hematopathologists who must distinguish between benign infection by the Epstein-Barr virus and Hodgkin's disease.

MICHAEL K. SAMOSZUK, MD
Irvine, California

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Tumor Suppressor Genes

The high frequency of cytogenetic, chromosomal, or single gene changes in most tumors had led to the concept that tumors represent a somatic cell genetic disease. With this realization, a major focus of tumor research has been to identify specific altered genetic factors and mechanisms that may be involved in tumor origin or progression.

A considerably increased understanding of tumor cell growth has come from the study of oncogenes, about 40 of which have been described. These oncogenes represent, in most instances, hyperactive deregulated states of normal cellular proto-oncogenes. Their altered states appear to be associated with increased tumor cell growth. At the cellular level, oncogenes appear to act in a dominant fashion. To date, however, mutations of the proto-oncogenes have not been associated with inherited tumors.

More recently, there has been evidence that a loss of function of certain genes may be associated with tumor growth. These have been variously called tumor suppressor genes, recessive oncogenes, antioncogenes, and growth-suppressing genes. Part of the reason for these several terms is that the normal function of these genes remains largely unknown. In contrast to the oncogenes, these tumor suppressor genes tend to be associated with tumors that are inherited in an autosomal dominant manner but that, at the tumor cell level, behave as recessive traits in that the loss of their function is associated with the tumor cell growth.

The prototype of tumor suppressor genes is the ret-

inoblastoma gene. The risk for this tumor to develop may be inherited in an autosomal dominant manner due to a mutated gene on chromosome 13. Based on characteristics of the tumor, many years ago, Knudson proposed a two-hit theory for the development of this tumor. According to this theory, one of the mutations in the inherited form of the tumor is inherited and requires only a second mutation to occur in any affected cell. With the sporadic form, it requires two new mutations to occur in the same cell. The subsequent studies with retinoblastoma have supported this hypothesis. In the retinoblastoma tumor, there is evidence for loss of function of both alleles at the retinoblastoma locus. This can occur through a variety of mechanisms including molecular mutations in the genes, somatic cell chromosome segregation, and somatic cell crossing over. In the inherited form of this tumor, the normal allele is altered or lost, resulting in a loss of the heterozygous state for the tumor-producing allele and the normal allele. One continuing perplexity is that in the inherited form, the persons are also at an increased risk for other tumors—such as osteosarcomas and small cell lung carcinoma—to develop later in life. In these other tumors, the retinoblastoma gene is also altered so that there is a loss of its function in these tumors as well. More recent studies have suggested that the normal product of the retinoblastoma gene can bind to oncogene products of DNA tumor viruses and that the product also appears to bind to cellular DNA. There has also been an indication that phosphorylation of the retinoblastoma protein is associated with cell growth and that the unphosphorylated state is associated with a lack of cell growth.

Following the retinoblastoma story, a second tumor which was studied for a loss of heterozygosity is the Wilms' tumor, which is sometimes associated with a partial chromosome deletion of the short arm of chromosome 11. Examination of the tumor cells indicated a loss of heterozygosity for markers on the short arm of chromosome 11. Recently a gene from this area has been isolated that appears to have the characteristics of the Wilms' tumor gene. The story here, however, may be more complicated in that in at least one form of the inherited tumor, the inherited gene does not seem to be in this area. Nevertheless, the approach of using the loss of heterozygosity in tumor cells has been extensively pursued, and, in a number of tumors, there does appear to be a loss of heterozygosity, suggesting that tumor suppressor genes may be located in the involved chromosomes or regions of chromosomes. These include the following tumors, with the loss of heterozygosity for the specific chromosome region noted in parentheses: melanoma, neuroblastoma (1p); breast carcinoma (1q); small cell lung carcinoma, renal cell carcinoma (3p); familial polyposis coli (5q); rhabdomyosarcoma (11p); multiple endocrine neoplasia (11q); colon carcinoma (17p); colon carcinoma (18q); and acoustic neuroma (22q).

Whereas only a small percentage of tumors are inherited as a simple mendelian trait, there are both inherited and sporadic forms of tumors, and these appear to be histologically indistinguishable. These studies and those noted earlier in the study of retinoblastoma suggest that at the somatic cell level, some of the same genes may be involved in the development of both inherited and sporadic forms of tumors.

These recent advances are leading to an increased understanding of which genes contribute to tumor development and the mechanisms that may be involved. Such understanding should lead to the development of preventive measures, earlier tumor detection, and, therefore, improved treatment and management of tumors. For example, improved genetic counseling has resulted from the recognition of the retinoblastoma gene. This clearly is only the beginning of the story, and there is every reason to expect that the role of tumor suppressor genes will become increasingly clear as our study of them expands.

ROBERT S. SPARKES, MD
Los Angeles, California

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Analysis of Solid Tumors by DNA Cytometry

DNA CYTOMETRY of a solid tumor provides information about its genetic composition (DNA ploidy) and its rate of cellular proliferation (S-phase fraction). These properties relate importantly to the clinical behavior of a malignant neoplasm—to its potential for metastatic recurrence, to the rate at which it grows, and, on occasion, to its responsiveness to therapy. Their clinical significance is clearly established for breast, lung, colon, and ovarian cancers and less clearly for thyroid, prostate, bladder, and renal cancers and for malignant melanoma.

There are two different methods for DNA cytometry; each measures the DNA content of individual cells. In flow cytometry, the tumor first is disaggregated to give a monocellular suspension. The cells are stained for DNA with a fluorescent dye and then are measured individually as they stream through a laser beam. In image cytometry, the cells are on a microscope slide, either as a whole cell preparation, such as a touch preparation or a smear from a fine-needle aspiration, or as a section cut from a paraffin-embedded tissue specimen. The slide is stained for DNA, and an automatic microscope system is used to measure the nuclear stain content of several hundred cells. For either method, measurements are displayed as a frequency distribution histogram in which the X axis represents DNA content and the height represents the number of cells having that DNA content.

Flow cytometry is the more commonly used method. Tens of thousands of cells are measured within minutes to give smooth and precise histograms that readily lend themselves to formal mathematic analysis. Its reliability, however, is limited by the need to dissociate the tumor. The flow specimen may contain many normal cells from adjacent nonmalignant tissue and from stromal, endothelial, and inflammatory components of the tumor itself. Thus, it is possible for the DNA histogram of a tumor to reflect primarily the normal rather than the malignant component.

Image cytometry is much slower and more labor-intensive than flow cytometry. Fewer cells are measured, and so the DNA histogram lacks the precision of a flow histogram. When sections are measured, the resolution is degraded still further because the section will cut through nuclei at random levels so that varying portions of nuclei are included within

the thickness of the section. Nevertheless, image cytometry is similar to conventional microscopic analysis, and so it is possible for the operator to identify each measured nucleus. Thus, while the DNA histogram may lack the resolution of flow, it can be relied on to represent only malignant cells and to be free of contamination by nontumorous cells.

DNA histograms are analyzed first for DNA ploidy by locating the major peak of the histogram—the DNA content shared by most of the cells. If this value is the same as that for normal tissues, then the tumor is DNA diploid; otherwise, it is DNA aneuploid, with a DNA index that is the ratio of the tumor value to the normal value. Flow or image cytometry reliably detects a deviation of 10% from normal.

Further analysis of the DNA histogram estimates the fraction of tumor cells that are in the S phase (synthesizing DNA). The DNA content of S-phase cells is intermediate between the major histogram peak (postdivision resting cells) and the peak located at twice this DNA content (predivision and dividing cells). The S-phase fraction relates directly to the rate of cellular proliferation—the higher the fraction, the more rapidly the tumor is growing. Estimating the S-phase fraction from the DNA histogram is difficult, however, and the results become unreliable if the preparation contains much nuclear debris or if the tumor has aneuploid populations of cells.

The usefulness of DNA cytometry in evaluating most solid tumors is extensively documented in studies using either flow or image cytometry. Many of these studies are retrospective, using archival paraffin-embedded tissue blocks. Thick (50 μm) sections are cut from the block and then are dissociated to obtain isolated nuclei for either flow or image cytometry. Such studies show that DNA aneuploidy and high S-phase fractions are usually associated with tumors of high clinical stage, high histopathologic grade, and generally poor prognosis. The independent diagnostic and prognostic powers of DNA cytometry become particularly important in low-stage tumors. For example, even low-stage breast, thyroid, or prostate cancers that show DNA aneuploidy or a high S-phase fraction have a high probability of establishing distant metastases whereas comparable DNA-diploid, low S-phase tumors are unlikely to metastasize. The results of DNA cytometry then provide clinicians with relevant information about the potential aggressiveness of the cancer.

In summary, DNA cytometry provides important diagnostic and prognostic information for the evaluation of solid tumors. This is most clearly established for low-stage breast cancers but also is well documented for a broad range of solid tumors. DNA cytometry is not infallible, however. As with all new tests, its power and limitations should be clearly understood, and results should be interpreted cautiously within the context of the overall clinical and histopathologic picture.

BRIAN H MAYALL, MD
San Francisco, California

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Relationship of Amyloid to Alzheimer's Disease

THE CLINICAL DIAGNOSIS of Alzheimer's disease or senile dementia of Alzheimer's type is confirmed in suspected cases by a neuropathologist after a careful examination of brain sections after necropsy. Of the microscopic lesions used to confirm the clinical diagnosis, all are present in normal aged brains but occur in exaggerated number and severity in the brains of patients with Alzheimer's disease. Three of these microscopic criteria have the classic tinctorial properties associated with β-pleated sheet fibrils, or amyloid. These are senile plaques, neurofibrillary tangles, and cerebral amyloid angiopathy or cerebrovascular amyloidosis. Of these, senile plaques and amyloid angiopathy are biochemically related, whereas the amyloid of neurofibrillary tangles appears to be composed of a different peptide. Whether the amyloidotic peptides found in excess in the brains of patients with Alzheimer's disease are a cause of the disease or simply an epiphenomenon is not clear. Nevertheless, brain amyloid is considered a marker of Alzheimer's disease or senile dementia of Alzheimer's and its presence important in confirming the diagnosis pathologically.

Senile plaque and microvascular amyloid are biochemically similar if not identical and consist of a unique peptide with a molecular weight of about 4,200. Since 1987, molecular biologic techniques have been used extensively to show that this peptide (known as the A4 or β-peptide) derives from a large precursor molecule composed of almost 700 amino acids. The identity of senile plaque and microvascular amyloid has been confirmed both biochemically and indirectly using immunohistochemical techniques at the light and ultrastructural levels. Some have suggested that immunohistochemistry using antibodies to the Alzheimer A4 or β-peptide is more sensitive in showing the earliest lesions of Alzheimer's disease than conventional silver stains or Congo red or thioflavin methods. Immunohistochemical studies have also shown that A4 or β-peptide is widely distributed in the brain, being found in areas not traditionally thought to be affected by the neuropathologic changes of Alzheimer's disease, such as the deep central grey matter, brain stem, and cerebellum, and it may even be seen in the gut and skin.

Current research on the biochemistry and molecular biology of Alzheimer A4 or β-peptide amyloid focuses on several areas. An intensive effort is aimed at establishing how the peptide is cleaved from its precursor (the A4P or APP molecule) and whether it originates in the brain, the peripheral circulation, or both. Although A4 or β-peptide is the most commonly observed amyloid in the central nervous system of patients with Alzheimer's disease or senile dementia of the Alzheimer's type, small amounts of γ-trace peptide (usually associated with amyloid angiopathy in Icelandic patients who have familial cerebral hemorrhage) have recently been found in the walls of the amyloidotic arterioles of patients with Alzheimer's disease. The biologic importance of this finding remains to be determined. Ideally, patients with Alzheimer's

disease might be segregated from patients with non-Alzheimer's dementia by the finding of elevated levels of A4 or β-peptide in the blood or cerebrospinal fluid—that is, a simple biochemical test could be used to confirm the presence of Alzheimer's disease. This is now done inferentially from clinical data and imaging studies, and the autopsy is used for definitive confirmation.

The A4 protein has been shown to be accumulated within lysosomes of certain neuronal populations in the brain, suggesting that proteolysis of the precursor with resultant deposition of the A4 or β-peptide within tissues may be a pivotal event in the neuronal degeneration that characterizes Alzheimer's disease both clinically and pathologically. In any event, research into possible mechanisms of processing of the A4 peptide into an insoluble form in the brain may lead to therapeutic strategies by which this processing can be engineered so that smaller amounts of microvascular and senile plaque amyloid are ultimately deposited within brain parenchyma. It remains an open question whether this will lead to stabilization or amelioration of the clinical signs and symptoms of Alzheimer's disease or Alzheimer's senile dementia.

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HARRY V VINTERS, MD
Los Angeles, California

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Stereotactic Brain Biopsy

THE MANAGEMENT OF MASS LESIONS of the brain continues to evolve with the increasing availability of stereotactic biopsy. Stereotactic biopsy is done through a small drill hole in the skull under local anesthesia and carries an extremely small risk of complications. The total time for obtaining a biopsy specimen is about two hours. Most patients come in for the procedure in the morning and leave the hospital after an overnight observation period. Stereotactic biopsy is capable of procuring tissue from virtually any location within the cranial cavity, including the third ventricle, hypothalamic region, brain stem, and posterior fossa. The availability of stereotactic biopsy allows the histologic diagnosis of any brain mass.

Basic mathematic principles are used to identify any point within the cranial cavity by means of three coordinates. The stereotactic instruments provide the three coordinates that guide the biopsy forceps to a target point determined on the radiologic image. With experience, representative material is procured in virtually all cases.

The pathologic interpretation is limited by the small size of the specimen, however. The accuracy of histologic diagnosis in experienced hands is about 90% overall. The use of smears is highly recommended as the primary means of making a diagnosis.

The accuracy and specificity of diagnosis are greatest for regionally homogeneous neoplastic lesions such as metastatic carcinoma, craniopharyngioma, oligodendroglioma, and malignant lymphoma. In these cases, the diagnosis depends only on the neurosurgeon obtaining tissue from the lesion and the pathologist making the correct diagnosis.

In regionally heterogeneous neoplasms such as astrocytomas and pineal germ cell neoplasms, the small size of the specimen creates theoretical problems. Here the diagnosis depends not only on obtaining abnormal material and the pathologic interpretation but also on regional differences within the neoplasm. Two solutions are available at stereotactic biopsy to overcome this problem. The first is to take several specimens from different target points in the lesion, increasing the tissue volume to provide a representative sample. This adds to the time and risk of the procedure but is an acceptable solution. The second is to interpret the biopsy in conjunction with full clinical and radiologic data to arrive at a clinicopathologic diagnosis. We use the latter method, and it has been our experience that a single specimen from an astrocytic neoplasm provides an accurate placement of the lesion in a three-tiered classification that is adequate for appropriate clinical management. The use of a single biopsy specimen in conjunction with tumor markers and radiologic features is adequate for most pineal germ cell neoplasms.

The lowest accuracy rate for stereotactic biopsy is attained when the biopsy specimen shows inflammation. Most of these will be nonneoplastic lesions. The rate of identifying a specific cause is low and requires careful handling of the tissue for immunohistochemistry (viral antigens), electron microscopy (viral particles), culture, and polymerase chain reaction (viral nucleic acid). Although a stereotactic biopsy specimen that shows inflammation is rarely from a neoplasm, we have had specimens interpreted as nonspecific inflammation turn out on a subsequent specimen to be malignant lymphoma, Hodgkin's disease, pineal germinoma, and anaplastic astrocytoma. It is prudent, therefore, to carefully evaluate inflammatory lesions diagnosed on stereotactic biopsy for the possibility of a neoplasm.

PARAKRAMA CHANDRASOMA, MD
Los Angeles, California

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Micrometastases in Melanoma

THE FIVE-YEAR SURVIVAL RATE for patients with melanoma spread to the regional nodes, the first site of metastasis for most melanoma patients, varies from 20% to 50% according to the number of nodes that contain metastatic melanoma and the micrometer measured thickness of the primary tumor.

Such evaluation underestimates the number of patients who will die of melanoma, in part because some nodes contain tumor cells that are not detectable on examination of hematoxylin- and eosin-stained sections, even when step sectioning is done. Immunohistochemistry with antibodies to S-100 protein or monoclonal antibodies to melanoma-associated epitopes showed that a conventional histologic assessment underestimates the number of tumor-containing nodes by 29% in patients with nodal spread of melanoma. A surprising 10% of patients with clinical stage I melanoma are in fact stage II when the nodes are examined by standard histologic techniques. A subsequent immunohistochemical assessment of patients whose nodes are negative on hematoxylin- and eosin-stained sections identifies 14% as having small occult micrometastases of melanoma in their nodes. The frequency of occult tumor cells increases with increasing thickness and depth of the primary tumor. Patients whose nodes contain micrometastases have a less favorable prognosis than those whose nodes are truly tumor free.

Studies with dye injected intraoperatively into the area of the primary tumor have shown that nodes that contain micrometastases lie nearest to the primary tumor on the direct lymphatic drainage pathway from it. Most patients have occult tumor cells in a single node, but as many as three nodes may be involved. The capacity to identify metastastic melanoma at a truly early stage and to delineate precisely the nodes most likely to contain micrometastases provides a new approach to the management of high-risk stage I melanoma. By using the dye-orientation approach, it is possible accurately to stage such tumors by selective lymph node biopsy and to limit the use of lymphadenectomy to persons with proven nodal tumor. This technique spares node-negative patients the complications of lymphadenectomy.

The immunohistochemical detection of micrometastases of melanoma will likely have important implications for staging, prognostication, and patient management. For these reasons immunohistochemical evaluation of lymph nodes is likely to become more widely applied. To validate the technique in the management of melanoma, a multicenter prospective trial is currently being organized. This management approach is unlikely to be limited to melanoma as occult tumor cells have been detected in patients with other forms of malignancy, including lung cancer, breast cancer, neuroblastoma, and vulvar cancer.

ALISTAIR J. COCHRAN, MD
Los Angeles, California

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Cytopathology—A Multiparameter Approach

CYTOLOGY AND FINE-NEEDLE aspiration biopsy (FNAB) are enjoying wide acceptance in this country as screening modalities, for diagnosis, for staging known malignant tumors, for assessing response to therapy, and for determining the need for further procedures. While the overall efficacy of cytologic and FNAB diagnosis when practiced by experienced professionals has been proved, histologic confirmation is advisable in many cases—such as the primary diagnosis of malignant lymphoma—before treatment is initiated. It is exciting to recognize that the application of ancillary studies including flow cytometry, immunocytochemistry, and image cytometry in cytology has now enhanced the accuracy of cytologic diagnosis and is contributing to the understanding of the biologic behavior of tumors.

Flow cytometry and image cytometry are used to quantitatively measure a variety of cell features including cytoplasmic and nuclear antigens and DNA content. Flow cytometric analysis is well established in evaluating hematologic specimens in which blood cell phenotyping and the quantification of various cell subpopulations are indicated. This method also has been applied successfully to cytologic specimens such as effusions, bladder washings, bronchoalveolar lavage fluid, cerebrospinal fluid, and cell suspensions of lymph nodes and tumors prepared from FNAB. Cell characteristics are assessed in a flow-based system in which thousands of cells are passed singly in a fluid stream through the tip of a flow chamber where scattered light and fluorescent signals are measured. The identification and quantification of cell surface antigens are helpful in evaluating lymphoproliferative disorders including non-Hodgkin's lymphomas. For example, the flow cytometric documentation of light chain restriction in a B-lymphocyte population is considered confirmatory of malignant lymphoma. In cases in which the cytologic diagnosis of malignant lymphoma is straightforward, flow cytometry also is useful in characterizing the lymphoma as of T- or B-cell origin or perhaps as one lacking B- or T-cell markers, data that generally correlate with the prognosis. Flow cytometry also may be used for DNA analysis. Combining flow DNA analysis for aneuploidy with a traditional urinary cytologic examination in patients with bladder cancer has been shown to dramatically increase the sensitivity for malignancy. This is just one example of the efficacy of a combined approach to diagnosis.

Immunocytochemistry as applied to cytologic smears and cytocentrifuge preparations may be used to assess cell antigens and hormone receptors. These studies may be done on direct smears, cytospins prepared from body fluids, and cytospins made from cell suspensions from lymph node and tumor FNABs. The use of immunoperoxidase techniques for cell surface marker studies has been extended to the identification of estrogen receptors in patients with breast cancer. Estrogen receptor immunocytochemical assay has been used successfully on cytologic smears prepared from FNAB. The method has been found to be highly sensitive and specific with good correlation with biochemical assays for estrogen receptor from the same tumor.

Image cytometry is used to measure cell components such as cell size, nuclear size, and DNA content in a microscopic slide-based system. Image cytometry may be applied to direct smears or cytocentrifuge preparations that are appropriately processed to stabilize DNA before hydrolysis. Generally carcinomas with an aneuploid DNA pattern have been found to behave more aggressively than those in the diploid range. This is particularly true in prostatic, bladder, and ovarian carcinomas.

Cytology now commands the use of an impressive array of ancillary studies that enhance cytomorphologic interpretation. While their use requires considerable experience, they

represent a valuable adjunct to diagnosis in the practice of cytology.

ROBERT W. ASTARITA, MD
La Jolla, California

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Alerts, Notices, and Case Reports

Palatal Myoclonus and Tinnitus in Children

GARY N. FOX, MD
MICHAEL T. BAER, MD
Reading, Pennsylvania

THE WORD TINNITUS is derived from the Latin *tinnire* for "ringing." Many reviews on the subject do not even attempt to define it.[1-3] A reasonable definition of tinnitus is any sound sensation perceived by the patient to have its origin inside the head, unrelated to external mechanoacoustic or electrical signals or, loosely translated, "ear noise."[4] In some surveys, tinnitus has been reported by nearly 100% of adults, with conservative estimates that 15% have reported spontaneous tinnitus lasting longer than five minutes, and 0.5% have tinnitus severe enough to affect their ability to lead a normal life.[4]

Tinnitus is subdivided into subjective tinnitus, which is apparent only to the patient, and objective tinnitus, which can also be heard by others. Objective tinnitus, in turn, has two broad sources, vascular and muscular, each of which can be further subdivided into specific diagnoses. Palatal myoclonus, a form of muscular tinnitus, was first described in the late 1800s[5,6] but has received no attention in the primary care or pediatric literature.

The literature on tinnitus in children is sparse[7]; even reviews on tinnitus often make no reference to its occurring in children.[1-3] The current data on subjective tinnitus in children come primarily from studies done by one investigator.[8,9] Objective tinnitus is as frequently neglected in review articles as childhood tinnitus.[2-4] In particular, muscular tinnitus and palatal myoclonus have been infrequently reported in children. Probably because of these infrequent reports, palatal myoclonus is thought to be rare in children.

Considering adults and children, fewer than 200 cases of palatal myoclonus have been reported in the medical literature.[10] This report is thought to be the 11th reported case in the English-language literature of palatal myoclonus in a preteenaged child and the first in the general medical literature. Previous reports have appeared in neurologic, otolaryngologic, and dental journals. We hope that literature attention to this disorder will stimulate the reporting of cases in young patients, providing a basis for the future counseling of patients and parents about prognosis and therapy.

Report of a Case

The patient, an 8-year-old girl, had nasal congestion and a sore throat unaccompanied by fever, cough, facial pain, headache, exanthem, or gastrointestinal symptoms. Pharyngeal culture revealed no group A, β-hemolytic streptococci. She was treated with a regimen of brompheniramine maleate (Dimetane). The patient returned 14 days later, reporting that her respiratory tract infection had resolved and new symptoms had developed. She noted "clicking" in both ears, more pronounced on the left. Her mother also heard the sound when near her. There were no fevers, facial tics, difficulty with verbalizing or swallowing, or neurologic symptoms. Immunizations, development, and school performance were appropriate for age. There were no known neurologic disorders in the family. The symptoms irritated the patient as she tried to fall asleep, but she and her mother were unsure whether the clicking persisted during sleep.

On examination, the patient was cooperative, verbal, and in no distress. The tympanic membranes, nose, and pharynx were normal. The soft palate showed clonic movements. A snapping sound, similar to flicking the edges of fingernails apart, was audible near the patient's ear without a stethoscope. The timing of the clicking varied, being sometimes faster and sometimes slower than the pulse, but clearly not synchronized with it. Neurologic findings, including cranial nerve and cerebellar testing, were normal. Tympanometry and audiometry were normal. Hoping that the palatal myoclonus would be transient, the parents initially elected to defer further investigation.

A month later the patient's symptoms and examination findings remained unchanged, but she had learned to stop the clicking transiently with a Valsalva maneuver. She and her parents requested therapy and consented to investigation. Computed tomographic (CT) scans of the brain with and without contrast agents and electroencephalography were normal. Therapy with a course of carbamazepine and then valproic acid produced no noticeable improvement.

The patient's status remained unchanged six months later. Her overall health and school and social function were normal. A magnetic resonance brain scan was declined. The family moved and was lost to follow-up.

Review of Cases in Children

Each childhood case that could be found in the English-language literature is reviewed. Some original reports are brief and incomplete. Most antedate the general availability of magnetic resonance imaging and some antedate the introduction of brain CT scanning.

Herrman and Brown described a 12-year-old boy in whom a viral syndrome with fever, malaise, and general aching developed, followed two months later by the onset of right-sided palatal myoclonus.[11] The sound was audible up to 76 cm (30 in) away from the patient. On neurologic examination, rapid alternating movements of the tongue and extremities were slowed and irregular on the right side. Except for these subtle findings on examination, the child was active and well. Laboratory, radiographic, and electroencephalographic studies were normal. The palatal myoclonus persisted unchanged during 15 months of follow-up. The report mentions no therapy.

Quarry reported a case of unilateral palatal myoclonus in a 6-year-old boy.[12] The patient had symptoms for four days, apparently precipitated by a bee flying into his left ear. The

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From the Department of Family and Community Medicine, Pennsylvania State University College of Medicine, Hershey (Dr Fox), and the Family Health Care Center, Reading Hospital and Medical Center, Reading, Pennsylvania (Drs Fox and Baer)

Reprint requests to Gary N. Fox, MD, Associate Director, Family Health Care Center, The Reading Hospital and Medical Center, Reading, PA 19603.

bee was quickly removed, but the noise, which had begun immediately, persisted. His mother could hear the noise and had noticed that it stopped during sleep. On examination, a clicking noise could be heard with the unaided ear 15 cm (6 in) from the patient's left ear but not near the right ear. The results of an ear examination, audiometry, and tympanometry were normal. With an impedance bridge recording the audible tinnitus from the left ear, cool air was directed at the left cornea, causing a powerful corneal reflex and the sudden and permanent cessation of the myoclonus. (The reflex arc for the corneal reflex is complex and is known to elicit the tensor tympani reflex and to influence several brain-stem centers.)

Jacobs and colleagues reported the case of a 7-year-old girl whose palatal myoclonus resolved spontaneously after 2½ years.[13] Her myoclonus began 12 months after general anesthesia for a tonsillectomy. Although her parents could hear the clicking as much as 15 cm away from the child, medical attention was not sought until a year after it started. The myoclonus persisted during sleep. Over the next year, the clicks became more erratic, ceasing first for minutes, then hours at a time. After another few months, the child could induce the palatal myoclonus with effort and concentration, but it did not occur spontaneously. Five years later, the results of an examination, electroencephalography, brain-stem auditory evoked responses, and brain CT scan remained normal; the young lady could still voluntarily induce the palatal myoclonus.

Litman and Hausman described the case of a 6-year-old boy with palatal myoclonus that lasted for ten months before resolving spontaneously.[14] Symptoms had been present for six months before the parents sought medical attention. Except for the palatal myoclonus, the findings of several investigations were normal, including examination by a neurologist, electroencephalography, non-contrast brain CT scan, audiometry, and tympanometry. During fiberoptic nasopharyngoscopy, impedance bridge recording, and motion picture photography, the patient's soft palate contraction was observed to be synchronous with the 60- to 70-click-per-minute frequency of the audible clicking. No therapy was used.

Tanaka and co-workers described the case of a 6-year-old boy whose palatal myoclonus disappeared with sleep,[15] which was thought to be unusual because of reports of palatal myoclonus persisting through natural sleep, barbiturate anesthesia, and deep coma (until death).[13] These authors were aware that adult patients had their palatal myocolonus completely disappear with sleep but were apparently unaware of Quarry's report of the 6-year-old boy whose palatal myoclonus did so.[12] Tanaka and associates' patient underwent a neurologic evaluation eight months after the symptoms began. In the interim, "sedatives" prescribed by the patient's family physician provided no relief. Cessation of the myoclonus during sleep was confirmed with fiberoptic nasopharyngoscopy. It was thought that this patient had some subtle neurologic signs—everted position of the right foot, incoordination of the left leg, and a rightward head slant—but cerebrospinal fluid studies, brain CT scan, electroencephalography, brain-stem auditory evoked responses, and otoneurologic tests were normal. The patient's course is not presented.

Toland and co-workers portrayed a man in whom, at age 34, a degenerative neurologic disorder began evolving after palatal myoclonus initially developed at age 5.[6] He had a history of seizure disorder, but the authors do not describe any anticonvulsant therapy. The patient's initial evaluation included a neurologic examination, comprehensive blood testing, thyroid tests, serum protein electrophoresis, syphilis serology, chest radiograph, brain CT scan, and electroencephalography. Electromyography of the palate was the only test eliciting an abnormality, as it objectively recorded the palatal myoclonus. After two years, the patient returned with progressive weakness and dyspnea, becoming wheelchair bound and exhibiting difficulty with speech and respirations. During fiberoptic nasopharyngoscopy, it appeared that the palatal myoclonus contributed to the respiratory difficulty because of involvement of the adductors of the larynx in the myoclonic contractions, producing forced closure of the true vocal cords. The nature of the progressive neurologic process was not specified, but it was speculated that the palatal myoclonus was a harbinger of the progressive neurologic disorder.

In a case reported by Baram and colleagues, a child was treated for acute lymphocytic leukemia with a regimen that included intrathecal methotrexate, cranial irradiation, and prednisone.[16] After a mild respiratory tract infection and a dose of intrathecal methotrexate, rhythmic "blinking" contractions of the orbicularis oculi muscles developed, followed about a week later by facial and palatal myoclonus. Encephalopathic findings developed the following week, and viral cerebrospinal fluid cultures yielded a picornavirus. Myoclonic activity unresponsive to medications developed in the right hand, foot, face, and left shoulder. The myoclonus resolved, but the patient had a residual right hemiparesis.

Siegel reported the case of a girl whose palatal myoclonus began at age 4.[5] The child had febrile seizures in infancy and a tonsillectomy at age 3. She believed an insect flew into her ear at the time the myoclonus started, but no foreign body was ever recovered. A diagnosis in this apparently healthy, active child was first made at age 12, eight years after onset, when she sought routine dental care. After examination by a neurologist showed no abnormalities, the youngster had bilateral second-division trigeminal nerve blocks with lidocaine hydrochloride, which decreased the audible tinnitus for about 45 minutes. The child and parents refused further diagnostic tests and therapeutic trials.

East and Hazell mention, but do not fully describe, an 11-year-old child with symptoms of palatal myoclonus for four years.[16] This child was treated with a tone-producing tinnitus masking device that, according to the report, produced an immediate symptomatic response. The palatal myoclonus was completely abolished after four weeks of therapy. The child remained symptom-free during five years of follow-up without the subsequent use of the masking device. The extent of investigation and previous therapies were not specified. East and Hazell studied this therapy after using a masking device—a common therapy for distressing cochlear tinnitus—in a patient with both cochlear tinnitus and palatal myoclonus. Unexpectedly, this patient reported a dramatic improvement in both her subjective tinnitus and palatal myoclonus.

Coles and co-workers, while describing a spectrum of patients with objective tinnitus, mention an 11-year-old girl who had experienced palatal myoclonus intermittently in each ear for seven months before diagnosis.[17] Her symptoms

disappeared during sleep and were aggravated by stress. They reportedly resolved after an additional ten months, during which she received psychiatric therapy.

Discussion

Subjective tinnitus, apparent only to the patient, is reported (when specifically sought) by 29% of healthy children having routine examinations.[8] Only a fraction of these children are bothered sufficiently by tinnitus to complain openly, but children can clearly describe tinnitus when questioned. Mills and colleagues thought an explanation for children's acceptance of tinnitus might be that their less well-developed sense of body image allowed them to perceive it as a normal experience.[8] Mills and Cherry found a 29% incidence of tinnitus among children with sensorineural hearing loss,[9] the same percentage Mills and associates found in their later study of children without ear disease.[8] Therefore, it is uncertain whether the presence of strictly defined high-pitched subjective tinnitus (likely to be of cochlear origin) has any discriminatory value in predicting ear disease in children. In contrast, clicking, cracking, and popping sounds may indicate air and fluid in the middle ear.

Thought to be comparatively rare, objective tinnitus can be heard by other observers—some authors specifically require the physician—in addition to the patient. Objective tinnitus has also been called extrinsic tinnitus or tinnitus of extracochlear origin, in contrast to subjective tinnitus, which has been equated with intrinsic tinnitus or tinnitus of cochlear origin.[1] In the broadest sense, objective tinnitus represents all body noise loud enough to impinge on consciousness. As such, it represents true sound energy rather than sound sensation. A high level of continuous baseline body noise exists from speech, respiration, normal vascular pulsation, motion of the neck and temporomandibular joint, and swallowing and other muscular activity, most of which is effectively suppressed most of the time. Defined in clinically useful terms, objective tinnitus is due to either an increased loudness of normal sounds or the production of abnormal sounds in structures in or near the ear.

Objective tinnitus has two identified sources, vascular and muscular. The sounds in vascular tinnitus can usually be determined to coincide with the pulse, to accelerate with exercise, and often to diminish with pressure over the lesion or by compression of the ipsilateral carotid artery.[18] The sounds in muscular tinnitus are unrelated to the pulse, usually have a clicking or snapping quality, and are higher-pitched than the vascular sounds. The rhythmicity of the muscular clicking may vary in an individual patient and varies among patients, with reported rates from 10 to 300 per minute.[14] Palatal myoclonus may disappear when the mouth is opened widely, making the diagnosis more difficult for an unsuspecting clinician.[18] Differentiating between vascular and muscular objective tinnitus is usually based clinically on the character of the noise, its relationship to the pulse, and its alteration when activating the pharyngeal muscles. Case reports of muscular tinnitus outnumber those of vascular tinnitus. In both children and adults, objective tinnitus appears much less prevalent than subjective tinnitus.

The rarity of vascular tinnitus may be surmised from a review by Wengraf,[19] who was able to identify only 40 cases in the English-language literature between 1900 and 1966. Arteriovenous fistulas, which are often of traumatic origin, and arteriovenous malformations in the posterior fossa are the primary causes of vascular tinnitus.[18,19] Arteriovenous malformations usually involve branches of the occipital artery and transverse sinus because there are numerous communications between these vessels. Intracranial aneurysms may rarely cause vascular tinnitus, although the overwhelming majority of these lesions are not audible to the patient. These aneurysms may be audible to the physician with a stethoscope, however.[19]

Tinnitus of muscular origin may arise from the rhythmic contraction of any of several muscles in the ear and throat. Contractions of the tensor tympani muscle or stapedius muscle may cause a sensation like a butterfly or insect flapping deep within the ear—described by the patients of Siegel and Quarry.[5,12] Larger muscles near the eustachian tube, the tensor veli palatini and levator palatini, may also contract, causing clicking noises. These muscles may contract independently or together.

Why these muscles contract spontaneously is unknown. Causes surmised from case reports (including those in adults) have included whiplash injuries; injuries to the posterior fossa; influenza; operations on the ear, nose, or throat; degenerative diseases; multiple sclerosis; central nervous system infections such as syphilis or encephalitis; shock; neoplasms; vertebral artery and other aneurysms; trauma; barotrauma; psychogenic factors; hereditofamilial tremor; and "idiopathic" causes.[6,14] Because of these associations, most authors regard palatal myoclonus as a symptom rather than a disease.

The primary disorder in palatal myoclonus appears to involve the olivocerebellar midbrain relay system.[6] Supporting this hypothesis, stimulation in the region of the inferior olive in monkeys produces myoclonic retractions of the palate.[20] A hypothesis for the physiologic mechanism underlying palatal myoclonus is denervation supersensitivity. Because of the time needed for denervation to occur, this hypothesis would explain the lag time between an event—that is, trauma or infection—and the appearance of the movement disorder.[21] Another postulate is that a hypersensitive reflex arc involving the mandibular nerve causes palatal myoclonus.[16] No pathologic data are available to support these hypotheses.

Therapies tried for palatal myoclonus (mostly in adults) have included psychotherapy, biofeedback, acupuncture, masking procedures using external noise, drugs, interruption of neural arcs (otic ganglion blocks, local anesthesia), and the induction of vigorous reflex responses. Drug therapies have included sedatives, anticonvulsants—clonazepam (Klonopin), carbamazepine (Tegretol), valproic acid (Depakene)—antiarrhythmics, and trihexyphenidyl (Artane). Surgical therapies have included ventilating tubes, sectioning of stapedial or tensor tympani muscles or both, and operative procedures to create a continuously patent eustachian tube. Currently there is no definitive or clearly preferable initial therapy.[5,14,22] The induction of a strong corneal reflex by a jet of cool air would appear reasonable to try. If reproducible by other investigators, the success of tinnitus masking devices reported by East and Hazell[16] promises a first-line therapy without the risks of drugs or a surgical procedure.

A review of the cases reported in children indicates that years may intervene between the onset and the diagnosis of palatal myoclonus and that a diagnosis may be incidental,

such as during a routine dental visit. In fact, the rapidly progressive neurologic disease in the patient with a 29-year history of palatal myoclonus may have been unrelated to the palatal myoclonus.[6] Not infrequently, patients (and parents) seem to be less concerned about the symptoms than their physicians, occasionally refusing suggested diagnostic tests and therapies. This behavior is contrary to the frequently encountered parental insistence to do more testing than is appropriate for many minor ailments, suggesting that patients and parents consider isolated palatal myoclonus a benign nuisance rather than a serious illness.

It is also apparent that a "typical" profile of palatal myoclonus in children has yet to emerge. In at least two children, including our patient, symptoms apparently developed after viral infections. (Examples of established relationships between infections and subsequent noninfectious neurologic disturbances include the Guillain-Barré syndrome following a viral illness, acute cerebellar ataxia in children following a viral illness, and Sydenham's chorea following streptococcal pharyngitis.) Two other children had tonsillectomies about a year before symptoms developed; postulating a relationship is tenuous. In at least two patients, symptoms resolved spontaneously without sequelae, another child appeared to be permanently cured by the induction of a massive corneal reflex, and still another had resolution after using a tinnitus masking device. At least two children had no myoclonus during sleep. Therapies have also varied widely with varying reports of success.

Recently reported cases of palatal myoclonus in children have focused on what authors considered to be atypical features, such as the disappearance of the myoclonus during sleep—which may prove to be common in isolated palatal myoclonus—its association with encephalitis, a case cured by vigorous corneal reflex stimulation, and the spontaneous resolution of palatal myoclonus. Whether this reflects an editorial bias (rejecting submissions of "typical" case reports), an author bias (the failure to report cases assuming the rejection of typical cases), or an absence of cases is unknown. If typical cases are not published, they may be more frequent than anticipated by the attention afforded in the literature.

Recent evidence suggests that palatal myoclonus is not widely recognized, particularly in children. In the *New England Journal of Medicine,* a pediatric cardiologist related his own frustration seeking relief from objective muscular tinnitus, during which time he "puzzled several authorities."[23] As recently as 1986, Baram and co-workers thought that "only one other child with palatal myoclonus has been reported."[21] If the condition is unrecognized, it is likely to be underreported.

In addition, it is possible that some patients ignore or suppress the symptoms of palatal myoclonus, similar to the suppression of the noises of chewing, swallowing, and cardiovascular activity. Other patients may fail to report their symptoms for fear of a devastating diagnosis or a psychiatric diagnosis. As postulated in subjective tinnitus, children may perceive objective tinnitus as normal and fail to report it. These factors would also lead to an underestimated prevalence of palatal myoclonus. If symptoms are first uncovered when these patients seek care for unrelated reasons, as illustrated by the diagnosis during routine dental care eight years after onset, spurious associations may occur, especially if the unrelated illness is neurologic.

Concluding Comment

In adults, authors have proposed that

> when myoclonus of the palate appears within a broader neurological complex, it is caused by an organic disease. Palatal myoclonus, when it appears as a solitary symptom, is of entirely different character. . . . The disease did not progress (in contrast to the evolutive character in the former group) and no additional symptoms appeared, even though the condition was in the majority of cases of long duration.[20(p395)]

For example, some affected adults have normal and others have abnormal brain-stem auditory evoked potentials, indicating that palatal myoclonus may be associated with either discrete lesions (isolated palatal myoclonus) or with diffuse or multifocal lesions (non-isolated palatal myoclonus) of the brain stem.[24] Although it is premature to conjecture that this pattern extends to children based on only ten case reports, most of the pediatric patients had a benign, nonprogressive course over many years. Brain CT scanning (with and without contrast agents), electroencephalography, spinal fluid analyses, audiometry, tympanometry, electromyography, brain-stem auditory evoked responses, fiberoptic nasopharyngoscopy, and other tests and procedures have been unproductive in children with isolated palatal myoclonus (otherwise normal examination). Much of the literature on this topic antedates modern brain imaging techniques, tempering any conclusions about what currently constitutes an appropriate evaluation of isolated palatal myoclonus. If accumulated experience, especially reports including long-term follow-up, proves isolated palatal myoclonus to be a benign disorder, children may be spared unnecessary intensive investigation.

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Bilateral Tension Pneumothoraces After Acupuncture

ROBERT S. WRIGHT, MD
Los Angeles, California

JEFFREY L. KUPPERMAN, MD
MYRON I. LIEBHABER, MD
Santa Barbara, California

During the past 20 years, acupuncture has become an increasingly popular "alternative therapy" for a variety of illnesses. While viewed by many as a useful adjunct for musculoskeletal conditions, it is also used by some practitioners for systemic illnesses, including asthma. Physicians should be aware of the purported justifications and possible complications of acupuncture therapy for asthma. The following report of bilateral tension pneumothoraces in a pregnant asthmatic patient receiving acupuncture demonstrates the need for this awareness.

Report of a Case

The patient, a 31-year-old woman, underwent acupuncture for the treatment of asthma during her third pregnancy. She had a history of childhood asthma but was asymptomatic from age 11 until age 27. During her second pregnancy, asthma recurred, and she has had intermittent exacerbations since. Multiple pollen allergies were treated with immunotherapy for three years preceding the third pregnancy.

About two weeks before undergoing acupuncture, she had a worsening of her asthma despite the use of theophylline, prednisone, subcutaneous epinephrine, cromolyn sodium, nebulized terbutaline sulfate, and a metaproterenol inhaler. In addition, tests confirmed that she was pregnant.

On the day of admission, she went to an acupuncturist who inserted standard acupuncture needles bilaterally in the tissues of her upper back. At the time of the needle insertions, she experienced severe pleuritic chest pain that persisted until she left the acupuncturist's office three hours later. Such severe dyspnea and tachypnea rapidly developed that she could not comfortably converse. She was seen at a nearby emergency department where a chest x-ray film showed bilateral pneumothoraces (Figure 1), but the abnormality was not recognized until she was transferred to our hospital for further evaluation.

She arrived at the hospital about nine hours after the initial acupuncture needle placement. She was in severe respiratory distress. Vital signs showed a blood pressure of 90/64 mm of mercury, a heart rate of 100 beats per minute, and respirations of 40 per minute. A pertinent physical examination revealed that the trachea was midline. She had bilateral costovertebral angle tenderness. Diffuse inspiratory and expiratory wheezing was noted, without friction rubs. Heart sounds were distant. There was no clubbing, cyanosis, or edema. The patient was given oxygen by nasal cannula at 6 liters per minute. An arterial blood gas determination showed a pH of 7.28, a P_{CO_2} of 40 mm of mercury, and a P_{O_2} of 101 mm of mercury. Bilateral thoracostomy tubes were immediately placed, and there was a rush of escaping air from each hemithorax. Her condition rapidly improved, but she still required standard bronchodilator therapy and steroids for asthma management. She was discharged to home after nine days and eventually bore a healthy full-term infant.

Comment

Several episodes of pneumothorax resulting from acupuncture have been reported worldwide. Carette and coworkers summarized most of the reports in 1984.[1] Most reports have mentioned unilateral pneumothorax, and we are aware of only four previously described episodes of bilateral pneumothoraces.[2-4] Tension pneumothorax has not been specifically described, although in one of the reported cases of bilateral pneumothorax, the patient died.[4] Also of note is the development of status asthmaticus in a patient with unilateral pneumothorax after acupuncture despite the placement of a thoracostomy tube.[1]

The case we have described is pertinent for several reasons. First, the patient believed that acupuncture would be beneficial for her asthma and that she could avoid the use of asthma medications during her first trimester of pregnancy. Second, the development of bilateral tension pneumothoraces was neither appreciated nor considered either clinically or radiologically by health care personnel initially seeing her at the referring medical facility. Finally, tension pneumothorax resulted, and this has been rarely described. The diagnosis in this case is based on the clinical description of air

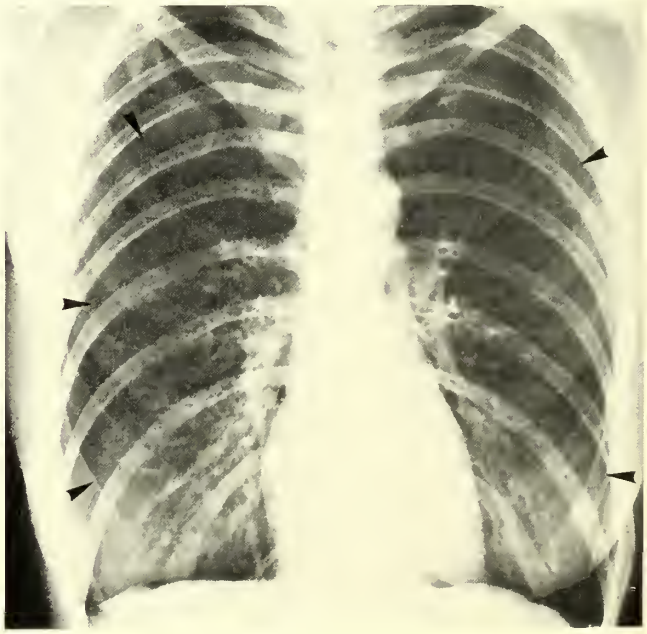

Figure 1.—A chest x-ray film taken several hours before presentation shows bilateral pneumothoraces. The arrows outline lung markings.

(Wright RS, Kupperman JL, Liebhaber MI: Bilateral tension pneumothoraces after acupuncture. West J Med 1991 Jan; 154:102-103)

From the Department of Medicine, Division of Pulmonary and Critical Care Medicine, UCLA Medical Center, Los Angeles (Dr Wright), and the Department of Medicine, Divisions of Pulmonary and Critical Care Medicine (Dr Kupperman), and Allergy and Immunology (Dr Liebhaber), Santa Barbara Medical Foundation Clinic, Santa Barbara, California

Reprint requests to Robert S. Wright, MD, Santa Barbara Medical Foundation Clinic, PO Box 1200, Santa Barbara, CA 93102-1200.

under pressure at the time of chest tube placement, her tenuous clinical condition, and the acidemia that reflected a lactic acidemia due to hypoperfusion. The lack of a mediastinal shift was due to the collapse of both lungs. The initial chest x-ray film certainly underestimated the degree of collapse because it was taken several hours earlier at the referring facility. We think cardiovascular failure was imminent and would have occurred without the placement of the chest tubes.

The principle of Chinese acupuncture is that inserting small needles along various channels or meridians restores the balance between yin and yang. The acupuncture needles are typically made of stainless steel and are 28 gauge in size or smaller. The so-called lung channel runs from below the clavicle, down the median aspect of the arm, and ends in the thumb.[5] Under usual circumstances, penetration of the skin along these points is harmless although possibly associated with minor discomfort. Many practitioners insert needles in other locations, however, including the upper back, as noted in the reports of pneumothorax cited. Pneumothorax can develop, particularly when the insertions are done during acute asthma attacks.

Although acupuncture has been shown by investigators to cause bronchodilation, possibly by cholinergic inhibition,[6,7] it is less effective than nebulized isoproterenol therapy, and the effectiveness is transitory.[8] Given this knowledge and the untoward effects of acupuncture reported herein, the use of this alternative therapy should be discouraged for the management of asthma. Patients who consider acupuncture for the management of their asthma should be informed of the possibility of life-threatening pneumothorax.

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Clinical Trial of Botulism Immune Globulin for Infant Botulism

TERESA L. FRANKOVICH, MD
STEPHEN S. ARNON, MD
Berkeley, California

WE WISH TO ALERT your readers to a new potential treatment of infant botulism, human-derived botulism immune globulin (BIG), that became available in California on January 1, 1991. The clinical trial of BIG is an efficacy (phase II) study sponsored by the Orphan Drug Program of the US Food and Drug Administration and the California Department of Health Services. Available laboratory data and experience with food-borne botulism suggest that prompt treatment of botulism yields the best outcome. To obtain BIG, physicians should contact the study office as quickly as possible when they suspect a diagnosis of infant botulism in their patient. The study's 24-hour telephone number is (415) 540-2646.

Infant botulism has a broad clinical spectrum of symptoms ranging from constipation and mild weakness to full paralysis requiring mechanical ventilation. Upon hospital admission the typical patient with infant botulism may have ptosis, a disconjugate gaze, expressionless facies, prominent head lag, diffuse hypotonia, and other neurologic findings. In spite of this, infant botulism may be difficult to recognize in its early stages, and, even today, the most common admitting diagnosis for these patients remains "rule out sepsis."

In the past two years, 68 patients with infant botulism were admitted to hospital in California, most of whom required treatment in the intensive care unit. The average length of hospital stay for these infants was 4.9 weeks, and total hospital costs exceeded $4 million. It is hoped that treatment with BIG will substantially shorten both the duration of illness and the cost of hospital stay for affected infants.

General inquiries regarding this disease or the BIG study can be directed to the Infant Botulism Prevention Program offices at the telephone number listed above, 8 AM to 5 PM (Pacific Standard Time), Monday through Friday.

(Frankovich TL, Arnon SS: Clinical trial of botulism immune globulin for infant botulism. West J Med 1991 Jan; 154:103)

From the SIDS—Infant Botulism Prevention Program, California Department of Health Services, Berkeley.

Reprint requests to Teresa L. Frankovich, MD, Project Director, BIG Clinical Trial, California Department of Health Services, 2151 Berkeley Way, Berkeley, CA 94704.

Commentary

Avocado

ARTURO ISLAS, PhD, *Stanford, California*

EDITOR'S NOTE: *Journals teach and stimulate in many ways. They present new information. They raise questions. They emphasize. They also may affect patient care by affecting physicians' feelings. This paper has affected reviewers not necessarily by presenting new information but by edging into their consciousness, by stirring their sense of humanity, by giving a new approach to hopelessness and handicaps. It is about teaching and about caring.*

"Avocado" is an adaptation of an address given at the Stanford University Class Day, June 1990. It is an excerpt from an unpublished novel, La Mollie and the King of Tears. *Dr Islas is Professor of English at Stanford. He has dealt with his own chronic illness for 30 years.*

Let me tell you a story—my favorite story about teaching, partly because life did not romanticize either the teacher or the student. On the contrary, this story illustrates what a wondrous and unpredictable process true learning can be.

One of the part-time jobs I found myself doing after earning my BA from Stanford in 1960 was teaching a public speaking class through the educational therapy program at the local and decrepit VA hospital in Menlo Park. In those days, only one psychiatrist per 100 patients was available, and the staff, as well as the inmates, were quite exhausted by institutional life. (Ken Kesey had worked as a nurse's aide in this very place a few years earlier and had drawn much of his material for *One Flew Over the Cuckoo's Nest* from his observations there.)

The story is told by a character who grew up in the barrio of South El Paso, my hometown. His name is Louie Mendoza, and he emerged from an assignment in a writing class I offered at the University of Texas four years ago. In this exercise, the students were asked to imagine someone completely different from them and to allow that person to speak in his or her voice for as long as seemed natural. I did the assignment myself. I thought of a Mr Martinez from the Educational Therapy class who, whenever I said his name during roll call, would respond in a thick Mexican accent, "He's not here," and mean it. Well, I guess in a way, he wasn't, but in another way that would flourish many years later, he was very much present. Mr Martinez was transformed through fiction into Louie Mendoza, and it's from his point of view that I wish to tell you the story. Two footnotes: the Mr Angel in the piece is roughly my fictional counterpart, and when Mr Mendoza uses double negatives, he does so to emphasize the negative.

"Ever been to one of them VA hospitals, man? The one I was in for a coupla months on my way back to Texas from Korea was somewheres in northern California. I was so outta the picture, the place coulda been in Alaska and I woulda just said, 'Fine. Leave me alone.'

"To add to the mess, the military bosses were making a change from one hospital to another and they decided to keep the hopeless cases in the old hospital and transfer the nonhopeless to the new 'facility.' My group was the last of the nonhopeless to be mixed up with the hopeless. I wouldn't of been able to see no difference then, man. I was feeling pretty hopeless just being in that godforsaken place, and I was too out of it to care.

"Mr Johnson, this King Kong albino they kept in maximum security mosta the time, was definitely one of the hopeless. I never did find out his first name 'cause we only got called by our last names in the educational therapy classes they put us through every morning. Mr Johnson came to them E.T. classes twice a week only, attached to a big Black Momma in her 30s who looked pretty strong. They was connected by a two-foot chain that started at her wrist and ended in a metal ring that was part of a harness Mr Johnson had to wear. It wasn't no straitjacket 'cause his hands were free, but it looked like one and probably felt worse than that to him.

"Mr Johnson never opened his mouth except once that I know about. He sat there them two hours of E.T.—even in a chair he looked six feet high—with his eyes all watery and drool oozing down his chin. He was so tranqued out, the aide had to wipe his face every five minutes.

"I can still see that poor E.T. teacher standing in front of that class of all-time losers. His name was Mr Angel, and he told us he was a graduate student trying to get through Stanford. He was supposed to teach us public speaking, even though half the class would never be let out in public again. That Mr Angel (I would say his name the Anglo way just to get his goat), he was real green, and we put him through the ropes, 'specially me.

"It wasn't hard to pretend that mosta the time in his class we didn't give a damn what he was saying 'cause we were all zonked out on something, mostly Thorazine. It's like this elephant tranquilizer that makes your skin turn green in the sun and all your teeth fall out before you're 35, if you get that far. Mr Johnson's skin was the greenest of all, and he was probably Mr Drool 'cause he was losing teeth right and left.

"So there I was to recover, man. To recover among the hopeless with no real help in sight and only Thorazine, nicotine, and educational therapy to keep us going.

"I never seen so many white rabbits in my life. The E.T. class had about 30 guys 18 to 80 years old and all veterans of

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From the Department of English, Stanford University, Stanford, California.
Reprint requests to Arturo Islas, PhD, Department of English, Stanford University, Stanford, CA 94305.

some war or other, including the wars with their families. A coupla young, early Vietnam kids were enrolled, but my favorites were the World War I and II guys 'cause they had some interesting stories to tell and made out like they knew how come they had killed other guys.

"Mr Johnson musta belonged to the World War II guys, but I never knew for sure. I ain't even sure he saw any of us with them milky blue bloodshot eyes that stared straight ahead. From the start, the aide let me sit next to him in E.T. He broke my heart, man, so I knew I had it back.

"I was probably the only one who caught on to what poor little Mr Angel was trying to do in them E.T. classes, though I made sure I never gave him no credit for it. Teachers always made me act crazy, no matter what, and I can't tell you how come. He was all ears, man, a real skinny dude with radar dishes on both sides of his head that picked up on everything.

"One of them mornings in about the third month of my 'recovery,' the Kid—desperate for some kinda reaction from us—brought two grocery bags fulla spices, fruits, and vegetables to E.T. He told us he wanted us to touch and smell what he was gonna pass around. He asked us not to taste or to tell him what we heard, just in case any of us schizos heard anything.

"That day, the Kid started talking to us about poetry and telling us that our five senses was the start of poetry. I knew then that he was studying something totally useless and was gonna remain a poor Mexican for the rest of his life. But I didn't say nothing and just let him go on and on about poetry.

"He told us that if we really put our minds to it, we could come up with the essence of whatever it was we was smelling or touching. 'Everyone can be a poet,' he was telling us suckers. 'But most of us are too tired or too sick or too lazy to find the poet inside and so we spend our lives in a doormat stage waiting for something outside ourselves to give us the words to talk about our own lives.'

" 'I ain't no doormat,' I said real loud.

" 'No, you're not, Mr Mendoza,' he said real bright. 'But I didn't say "doormat." I said "dormant." ' He told us what that meant, and I had to agree that in that room anyways, most everyone was pretty much asleep.

"I made like I didn't wanna play along, but when the bottle of sage got to me, the whole desert in bloom came into the room—I could actually see it, man, no lie—and I was 6 years old, and my mom was telling me not to play in the streets.

" 'Tell us what you're feeling, Mr Mendoza,' the Kid said in a real quiet voice. Me, I was Mr Dumb, not able to say nothin' and just staring at the sage all purple against the wall that divided the projects from the Border Highway.

"Next to me, Mr Johnson was holding on real tight to an avocado and not letting no one take it away from him. The guy on the other side of him kept elbowing him to pass it on. He musta been a new guy 'cause no one never touched Mr Johnson, man. He could kill.

" 'Leave him alone,' the Kid said. 'Keep passing around the other things and tell us what you feel. You just hang on to that avocado, Mr Johnson.' And he started writing down what the guys was saying like they was lines of poetry on the blackboard.

"There we were—a buncha grown crazy dudes—feeling fruits and vegetables, putting our noses in spice bottles, oohing and aahing away, and saying things like 'This peach feels like April' while the Kid wrote down every line and they got funnier and funnier 'til we were all laughing, even him, real laughing. Everybody except Mr Johnson.

"He sat there in the middle of it all with great big Thorazine tears rolling down his pitted, green face and with the avocado in both hands like he was holding an egg—real still and real tender. I could feel it. So could the aide 'cause she stopped wiping his cheeks.

"Then a silence—like the kinda silence you get when it snows in the desert and there ain't no wind—fell on one man after another when each of us seen that Mr Johnson was trying to say something.

" 'Ah. Voh. Cah. Doh. Ah-voh-cah-doh!' He made it seem like each part of the word was a Mayan god, and he did it real slow and quiet like he knew what he had in his hands and then real loud and quick like he was finding gold.

"For one long moment, all the guys woke up and nobody moved or talked—not even me. Then some smart aleck new to the joint started clapping real sarcastic, and the rest of the sheep joined in. The spell was broken.

"At the far end of the table, the Kid was trying not to cry outta frustration or happiness, I couldn't tell which, and Mr Johnson went back into the darkness inside himself. But it was a great moment, man, and I gotta admit I cried later for all the cuckoos in that place, 'specially Mr Johnson."

Editorials

Osteoporosis at the End of the Century

DESPITE THE CURRENT PROMINENCE OF AIDS, osteoporosis may well be the disease of the 1990s. A recent report from the University of Southern California Gerontology Center ranked osteoporosis along with Alzheimer's disease as potential "budget busters."[1] Kelsey estimated that osteoporosis cost the nation $8 billion in 1986.[2] Even if disease prevalence in the elderly population remains constant, the rising number of elderly will raise that cost manyfold over the next few decades. More worrisome are data from several European sources that indicate an alarming rise in the age-adjusted incidence of hip fracture over the past 30 to 40 years.[3-5] Whether similar increases are occurring in the United States is uncertain. We were already close to the world leader in the incidence of hip fracture, and it may simply be that Europe is catching up to us. Either way, osteoporosis—particularly hip fracture—will strain our resources, both monetary and professional. Thus, it is useful that THE WESTERN JOURNAL OF MEDICINE has chosen to reprint in this issue a major current review of this disorder.[6]

Riggs emphasizes the traditional view that osteoporosis consists primarily of decreased bone mass. Indeed, that approach is explicit in the very name we give the disorder. The clinical problem, however, is most directly fragility, not porosity, and structures engineers recognize that fragility has many origins. A decreased quantity of material is only one of them. Arrangement and connectedness of the material—architecture—is another. Equally important is the loading history of the member, expressed in its accumulated burden of fatigue damage.

We all lose bone with age, and, indeed, by the usual age of hip fracture, virtually everyone is more than two standard deviations below the young adult mean. But not everyone fractures. Differences in a propensity to fall and in injury pattern are one reason. A growing body of evidence indicates convincingly that lost connectivity and excess fatigue damage are also important contributors to the fragility that we diagnose clinically as osteoporotic fracture.[7-9] Women with spine compression fractures have been found to have significantly less connectivity among their trabecular structures than do persons without fracture but with the same degree of lost mass. And studies of patients with hip fracture have shown local decreases in remodeling[9] so that fatigue damage accumulates specifically in the region of the femoral neck. The causes are not understood, but both abnormalities mean that the involved bone loses strength out of all proportion to its loss in mass. In brief, most of the low-trauma fractures we call osteoporotic appear to have at least two osseous parents. Reduced mass is only one of them.

The professional community has been slow to accept these facts, in part because of its investment in the notion of decreased mass, and in part because fragility itself is not easily detectable. Indeed, most of our research and all of our therapy is directed at altering bone mass and density. The ultrasound-based methods appear to have promise in detecting fragility directly,[10] but experience with them is still limited.

The effort directed at measuring and preventing bone loss has not, of course, been wasted. If it takes two fragility factors to result in low-trauma fracture, then preventing either will prevent the fracture. So maintaining optimal bone mass, where that is possible, remains a sound stratagem. But mass alone is clearly not enough, as the recent fluoride trial illustrated.[11] Recognizing that fragility has other definable causes helps to understand the clinical reality better and promises additional opportunities to intervene as well.

Unfortunately, while the struggle goes on to understand the disorder, the number of already fragile persons increases yearly. Even if a magic bullet were discovered today, we are certain to reap a bumper crop of fractures whose seeds have long since been sown. A few simple stratagems—simple in concept if not equally easy to implement—may help mitigate this growing problem.

Most fractures are caused by trauma, even the fragility fractures that are associated with osteoporosis. Preventing falls is a sensible approach for the already fragile elderly. Another is dissipating the force of injury by soft tissue or other shock-absorbing material. Drop a glass tumbler on a concrete floor and it invariably shatters. With even a relatively thin carpet, it will usually bounce. Hip fracture is unusual in overweight persons, in part because the bone is stronger, but in part also because it is better padded. If we cannot pad our elderly, perhaps their environments can be padded.

Adequate nutrition is one potentially controllable factor contributing directly to bone strength or fragility. Hip fracture is more common and heals less well in those who are malnourished. A recent report from Geneva underscores the importance of paying attention to nutritional factors even in persons who have already suffered a fracture.[12] A related concern is the importance of adequate calcium intake in maintaining maximal bone mass as we age. Several studies now show that hip fractures are substantially less common in persons with high calcium intakes,[13,14] and even thiazide use—presumably through its calcium-sparing effect—is associated with reduced hip fracture risk.[15]

One of the recommendations of the 1984 National Institutes of Health Consensus Conference on osteoporosis was that postmenopausal women should receive calcium intakes of 1,500 mg per day.[16] This recommendation remains sound and certainly is better supported by scientific evidence today than it was then. Even 1,500 mg may not be enough for everyone, since absorption efficiency falls with age and since, with reduced solar exposure among the elderly, vitamin D status is commonly marginal or inadequate. It must be stressed that the reduced bone mass that is one of the contributors to osteoporotic fragility has many causes, just as does the reduced hemoglobin mass of anemia. Low calcium intake is only one of them, as iron deficiency is only one of the causes of anemia. But in both cases, it is a cause that something can be done about. It would not be realistic to expect that assuring an adequate calcium intake will prevent all age-related bone loss. Fortunately, our goal can be more modest: to prevent any calcium deficiency component of that loss.

There has been unfortunate confusion around this issue of calcium intake, largely because a high calcium intake does not prevent the loss of bone that occurs in the immediate postmenopause.[17] This loss is due specifically to estrogen withdrawal. In just the same way, calcium will not prevent a

loss of bone due to immobilization. Nevertheless, calcium supplements *will* prevent the loss of bone due to inadequate calcium intake. Our mistake has been to generalize from studies in the immediate postmenopause, which is dominated by the readjustments produced by estrogen withdrawal, to periods either earlier or later, for which there is ample evidence that a high calcium intake is bone sparing.[18-20]

Although it is never too late to start to assure an adequate calcium intake, it must also be acknowledged that the roots of the problem go deep. The building of an optimal bone mass, particularly during the teen years and young adulthood, is of critical importance. Many teenaged girls today have such low calcium intakes[21] that there is no possibility that they can repeal the law of the conservation of mass and make much of a skeleton from the raw materials they provide their bodies. It is today's teenagers with low calcium intakes who are likely to be our hip fracture patients in 60-plus years from now. We are doomed to a perpetual game of catch-up until we can implement effective populationwide strategies to increase the level of calcium intake. This is an achievable goal, just as years ago ways were found to increase intakes of such trace nutrients as fluoride and iodine. If one is tempted to think about this as medicating the population, it may be instructive to bear two facts in mind: the primitive human calcium intake—the one, presumably, to which our physiology is adapted—is well in excess of 1,500 mg per day[22]; and the natural food sources of our closest primate relatives provide them with diets containing roughly four times the calcium nutrient density of a typical first-world human diet.

Next, there is the importance of maintaining physical activity, both before and after a fracture. Our skeletons are, after all, mechanical systems, and the principal intrinsic stimulus to their self-maintenance is mechanical loading. Not only does physical activity help preserve bone mass, but it probably is an important factor in the maintenance of adequate remodeling, without which fatigue damage will accumulate. It is difficult to increase bone mass very much by increasing physical activity; unfortunately, it is easy to lose mass with inactivity. So maintaining load-bearing activity is critical.

Finally, a brief word about pharmacotherapy. Recent promising reports describing the use of bisphosphonates indicate that these agents may have a useful role in the management of patients who already have the disorder.[23,24] Many years of experience have been accumulated with their use in Paget's disease, and so their long-term safety is reasonably assured. They are, however, remodeling suppressors, and their long-term effects in persons who already have compromised skeletal strength will have to await further study.

Fluoride is another issue. Riggs is cautious, which is understandable, given his recently reported experience in which fluoride did not decrease fracture incidence despite a nearly 40% increase in bone mass.[11] The protocol for his study, however, dictated not by the investigators but by the sponsoring agency, called both for what is now recognized to be a toxic dose of fluoride and for administration in a form that is known to produce excess gastrointestinal irritation.[25] The high peak blood concentrations produced by such therapy may well produce a degree of osteoblast toxicity that lower, but more sustained, blood levels do not. Certainly they will produce areas of hypercrystallinity in newly deposited bone mineral that will result in bone of different mechanical properties from bone mineralized out of a medium with a lower fluoride concentration. Fluoride is now approved for the treatment of osteoporosis in at least eight European countries and should not yet be counted out of the running in the US.

ROBERT P. HEANEY, MD
John A. Creighton University Professor
Creighton University
Omaha, Nebraska

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Nitric Oxide, Nitrovasodilators, and L-Arginine—An Unusual Relationship

CERTAINLY ONE OF THE MOST interesting and potentially far-reaching discoveries that has taken shape over the past few years concerns a novel mammalian pathway that leads to the formation of nitric oxide from the amino acid L-arginine.[1] This unusual biochemical pathway brought together seemingly unrelated fields of research. Nitric oxide formation has now been found in a number of cell types, but the first and, until now, the most thorough characterizations have been in macrophages, endothelial cells, and cells of the central ner-

vous system. The action of nitric oxide generated through this pathway is dependent on the cell type that produces it. Endothelium-derived nitric oxide leads to vascular smooth muscle relaxation, and, although the debate continues, most of the evidence supports that nitric oxide is endothelium-derived relaxing factor (EDRF) and that it acts by activating the enzyme guanylate cyclase in smooth muscle tissue. In the central nervous system, nitric oxide acts in a manner similar to that from endothelial cells in that it signals an adjacent cell and in this case another neuron. Macrophage-derived nitric oxide is distinct in many ways from the other two cell types, and evidence supports a role for this nitric oxide in the cytostatic activity that is a critical function of these activated immune system cells.

The history of this pathway is relatively short and illustrative of the convergence of apparently disparate research areas. During the late 1970s, a number of key observations concerning guanylate cyclase were made whose overall importance and relationship to this pathway became clear later. In particular, Murad and colleagues showed that nitric oxide activates guanylate cyclase,[2] Craven and DeRubertis showed that this nitric oxide activation is dependent on heme,[3] Ignarro and co-workers found that nitric oxide leads to the relaxation of smooth muscle,[4] and Furchgott and Zawadzki showed that the endothelium was required for vascular smooth muscle relaxation.[5] Also in the late 1970s, a number of laboratories involved with studies of the brain contributed to the growing idea that nitric oxide activated guanylate cyclase and that arginine and glutamate stimulated guanylate cyclase activity as well. In the early to middle 1980s, studies carried out with macrophages provided some key pieces to the puzzle. In experiments related to the endogenous formation of carcinogenic *N*-nitrosamines, Tannenbaum and co-workers showed that mammals were capable of nitrate synthesis.[6] Continuing studies in that laboratory showed that nitrate urinary levels were significantly elevated after treating rats with immunostimulants such as lipopolysaccharide.[7] Then in 1985 Stuehr and Marletta determined that macrophages treated with lipopolysaccharide synthesized nitrite and nitrate,[8] and subsequent studies showed that lymphokines such as interferon gamma could also stimulate this synthesis.[9] The stage was set in 1987 and 1988 for the convergence of the findings in the central nervous system (CNS), endothelium, and immune system. Iyengar and associates and Hibbs and colleagues showed that the precursor for nitrite and nitrate in macrophages was L-arginine,[10,11] and, in addition, Iyengar and co-workers showed that the nitrite and nitrate were derived from the guanido group of arginine.[10] Hibbs and colleagues also showed that arginine was required for macrophage-induced tumor cell cytostasis.[12] The chemical identity of EDRF had been the subject of much speculation and research, but it was Moncada and associates who provided the first definitive proof that endothelial cells were capable of nitric oxide synthesis.[13] The solution instability of nitric oxide suggested that it was likely to be the intermediate that led to nitrite and nitrate in the macrophage studies mentioned above. Marletta and co-workers and Hibbs and associates provided direct proof that this was indeed the case.[14,15] Moncada and colleagues then showed that the endothelial cell nitric oxide was derived from L-arginine,[16] and Garthwaite and co-workers showed that nitric oxide was produced by glutamate stimulation of *N*-methyl-D-aspartate receptors.[17] It was now clear that the L-arginine to the nitric oxide pathway was the common theme in all of these observations.

An immediate outcome of these findings is that they provide a rational mechanism for the action of nitrovasodilators such as nitroglycerin. Nitroglycerin is known to decompose to nitric oxide under biologic conditions, and although the series of reactions is mechanistically complex and not completely understood, the reaction is facilitated in the presence of thiols such as glutathione. Therefore, nitroglycerin and related nitrovasodilators act by circumventing the enzymic generation of nitric oxide. It is particularly satisfying that the study of this pathway has led to an understanding of the mechanism of action of such an important class of drugs in use for more than 100 years and, perhaps more important, points the way toward the design of agents that could potentially mimic the pathway more successfully. As mentioned, there is not uniform agreement on the identity of EDRF. The debate has focused on the properties of EDRF generated from stimulated endothelial cells in a smooth muscle bioassay versus the action of nitric oxide and various *S*-nitroso compounds in the same bioassay. The answer will come from studies on the enzymology of the pathway in the various cell types, but at this point it appears that it is nitric oxide that is released by the enzyme. The solution decomposition of nitric oxide generates a number of products that readily nitrosate thiols and amines which can, especially in the case of *S*-nitroso compounds, cause smooth muscle relaxation.

The regulation and biochemistry of the pathway are two aspects under investigation at present. The results of these studies are likely to provide key pieces of information with regard to the potential for cell-type-specific drug interactions. Some important differences have already emerged where it is clear that the macrophage is distinct from the other cell types in a number of respects. Consistent with the function as a signaling agent, nitric oxide synthesis occurs in a burst in both endothelial and CNS cells. The activity in these cells requires calcium ion (Ca^{2+}), and a report of the enzyme purification from rat brain showed a requirement for Ca^{2+}-complexed calmodulin and a single polypeptide of 150,000 daltons.[18] Because of the similarities in the CNS and endothelial cell activity, it may well turn out that the endothelial cell also shows a calmodulin requirement. In macrophages the activity cannot be detected in untreated cells, but after stimulation and subsequent protein synthesis, the cells continuously synthesize nitric oxide. The activity in macrophages is enhanced by divalent metals with magnesium ion being the most effective; these metals are not required, however. In addition, the cofactor tetrahydrobiopterin has also been identified as a requirement in macrophages.[19,20] The most common role for this cofactor is in aromatic amino acid hydroxylation such as with phenylalanine hydroxylase. Experiments suggest that this is the function for this cofactor in macrophages. On the other hand, although there does not appear to be a low-molecular-weight cofactor involved in the CNS or endothelium, a relatively tightly bound pterin has not been ruled out. A number of arginine-related compounds have been shown to inhibit the reaction, most notably N^G-methyl-L-arginine, which inhibits the activity in all cells examined to date. L-Canavanine, however, appears to be a specific inhibitor for the macrophage and neutrophil, and, while not potent, it at least shows that selective inhibition is possible.

The stage is now set for exciting developments in the

application of this research to the development of new drugs. It is clear that substantial differences exist between the basic enzymology of the macrophage compared with that of the CNS and endothelial cells and in the regulation of the pathways in those cells. The extent to which these differences can be exploited will determine just how fruitful this area will be for drug development. It is difficult to see any advantage in the inhibition of the activity in endothelial cells, but inhibition of the activity in the macrophage may be useful in the treatment of endotoxic shock, inflammatory bowel disease, and arthritis and in cytokine therapy. The extensive use of the nitrovasodilators in the treatment of angina and, as brought out in the article in this issue by Ignarro, Ross, and Tillisch,[21] their potential in other cardiovascular diseases suggest that attention should be given to the development of new vasodilators with more controlled chemistry.

MICHAEL A. MARLETTA, PhD
Associate Professor of Medicinal Chemistry, College of Pharmacy
Associate Professor of Biological Chemistry, School of Medicine
University of Michigan
Ann Arbor, Michigan

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Lessons From the Practice

Surgical Aphorisms

STEVEN W. MERRELL, MD, *Rochester, Minnesota, and* JAMES M. McGREEVY, MD, *Salt Lake City, Utah*

Webster's dictionary defines an aphorism as "a concise statement of a principle; a terse and often ingenious formulation of a truth or sentiment (usually in a single sentence)." The following is a collection of aphorisms that we accumulated in the course of our surgical training. Some are serious, some are poignant, some are humorous, but the aphorisms also reflect the flair of individual surgeons and the nature of surgery as a discipline.

The original source of many aphorisms cannot be identified. Some of these have been uttered by our mentors or colleagues, and some have appeared in print in one form or another. When possible, we have attempted to credit persons who we believe to have generated the remarks, although it is likely that these sources have paraphrased or quoted physicians who preceded them. It may be true that "nothing is new under the sun," but, as Gide once said, "It doesn't matter that everything has already been said, because no one was listening." We hope that this effort will help illustrate and preserve an important part of our surgical heritage.

General Considerations

Zollinger: A good surgeon is a good internist who can also operate.

Halsted: The only recourse for an anesthetized patient against an incompetent surgeon is hemorrhage.

Anonymous: Never ask a surgeon whether you need an operation.

Anonymous: Pray to God, but be sure to choose a good surgeon.

Osler: To study the phenomenon of disease without books is to sail an uncharted sea, but to study books without patients is not to go to sea at all.

Anonymous: Nothing heals like cold, hard steel.

Anonymous: Every neurotic patient ultimately dies of organic disease.

Dock: The most important thing to remember about rare diseases is that they are rare.

Corollary: Common things occur commonly.

Anonymous: A clinical problem is more likely to be an uncommon presentation of a common disease than a common presentation of an uncommon disease.

Flemma: What you can do *for* a patient is infinitely more important than what you do *to* a patient. The art of surgery is to discover the difference.

Anonymous: There is no such thing as bowel function at the VA.

Anonymous:

- Be careful of your thoughts, they may break into words at any time.
- A closed mouth gathers no feet.
- No one betrays himself or herself by silence.
- Better to remain silent and be thought a fool than to speak up and remove all doubt.

Anonymous: A chance to cut is a chance to cure.

Anonymous: Mediocre doctors are always at their best.

Anonymous: When the only tool you have is a hammer, the whole world looks like a nail.

Lerner: There is more to a patient than surgeons can remove.

Carey: The only way to make a silk purse from a sow's ear is to start with a silk sow.

Wright (regarding cosmetic surgery): You can't make a silk purse out of a sow's ear . . . you can, however, make a better looking sow's ear.

Definitions

Profession: A group of individuals largely, if not solely, dedicated to preserving its own status.

Alcoholic: A person who drinks more than his or her surgeon.

Life of a surgeon: A constant and losing battle against obsolescence.

Confidence: The feeling you have before you understand the situation.

Logic: The art of going wrong, with confidence.

Academic: Very learned, but inexperienced in (or unable to cope with) the world of practical reality.

Academic "circles": Collections of people in a circle, each patting the back of the person in front of him, and never looking outside the circle (Carey).

Drowning: Leading cause of death in surgeons; they think they can walk on water, and when they sink, they can't keep their mouths shut! (Flemma).

Hedge: The official plant of radiologists.

Academic Surgery

Wangensteen: Never turn down a hospital committee appointment, and once appointed, never go.

Expressions describing a surgeon's experience in academic circles:

"I've seen *any* number of these . . ." ($N \geq 0$)

"In my experience . . ." ($N \geq 1$)

"My personal series . . ." ($N \geq 2$)

"I've seen this in patient after patient after patient . . ." ($N \geq 3$)

"In my experience of somewhat less than 100 . . ." ($N << 100$)

Donsen: Specialists learn more and more about less and less until, finally, they know everything about nothing. Gen-

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From the Department of Surgery, University of Utah College of Medicine, Salt Lake City. Dr Merrell is currently with the Section of Vascular Surgery, Mayo Clinic, Rochester, Minnesota.

Reprint requests to Steven W. Merrell, MD, Section of Vascular Surgery, Mayo Clinic, Rochester, MN 55905.

eralists learn less and less about more and more until, finally, they know nothing about everything.

O'Leary: Give medical students a 50/50 random chance of reaching the correct answer, and they will almost always be wrong.

Bahnson: It's easier to get someone to work with you than for you.

Confident resident in OR: This is the way I *always* do it.

Ferguson: Just when residents become good enough to assist, they want to be the primary surgeon.

Mabry's Law (of referral practice): The easy ones go across the street.

Ravitch: When residents answer a question with a question, they almost certainly do not know the answer.

Surgical Judgment

Bernard: Experiments are not performed to confirm our ideas but rather to control them.

Menchen: To every complex problem, there is a solution that is neat, simple—and wrong.

Maier: If facts do not conform to theory, they must be disposed of.

Von Helmholtz: The greatest derangement of the mind is to believe in something because one wishes it to be so.

Phinagle's Credo: Science is truth. Don't be misled by the facts.

Anonymous: There are often more doctors writing about rare diseases than there are patients dying of them.

Anonymous: The mind is like a parachute. It only functions when it is open.

Bernstein: If something is worth doing well, someone has probably already done it.

Bahnson: Not everyone needs an operation before he or she dies.

Ravitch: When the primary indication for an operation is pain, that's exactly what you'll get.

Lord Moran (Churchill's physician): The feasibility of an operation is not the best indication for its performance.

Anonymous: When all else fails, do not allow skin to stand between you and the diagnosis.

Hawkin's Law: The lesser the indication, the greater the complication.

Anonymous: It takes only a few years to learn when to enter the abdomen but many years to learn when to stay out.

Rubinstein: It is hard to improve on the asymptomatic state.

Carey: Patients with GI disease have GI symptoms.

Anonymous: It takes more wisdom to profit from good advice than to give it.

Osler: You should not prevent patients from getting well on their own. *(Primum non nocere)*

Bahnson: Don't trouble trouble unless trouble troubles you.

Richards: Bad experiences are the result of poor judgment, but good judgment is the ultimate result of bad experiences.

Intraoperative Considerations

Carey: All postoperative complications begin in the operating room.

Culbertson: If you don't know what you're cutting, don't cut it.

Gough's Exception (for oncologic surgery): I don't know what it is, but it goes with the specimen.

Kuykendal: When you don't know what you're doing, be real careful.

Mayo: See what you are doing, and leave a dry field.

Gay: The greatest enemy of "good" is "better." The ultimate enemy of "good" is "perfect."

Wright: If it ain't broke, don't fix it.

Anonymous: Beware of the surgeon who is great at getting out of trouble.

Murphy's Laws (for surgeons):

- If anything can go wrong, it will.
- If it looks easy, it will be difficult. If it looks difficult, it will be damn near impossible.
- If everything seems to be going well, you probably overlooked something.

Roundsmanship

"It's pending."
"The computer's down."
"The path isn't back yet."
"My alarm didn't go off."
"My beeper was dead."
"My beeper was on, but they never paged me."
"The specimen was lost."
"The patient didn't tell *me* that."
"If I've done anything to be sorry for, I'm willing to be forgiven."
"The patient died of old age—he just happened to be in the hospital."

Famous Last Words

Shunway: All bleeding stops.

The broken suture: It wasn't the suture's fault, the jerk on the end did it!

Anonymous: Charcoal doesn't bleed.

Corollary: If it's black, we won't be back.

Anonymous: It was dry when we closed.

Hudson: When you're through, quit!

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Strauss MB (Ed): Familiar Medical Quotations. Boston, Mass, Little, Brown, 1968

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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Series' Editors

INSTRUCTIONS FOR AUTHORS

Our readership represents all specialties of medicine. We wish to receive and publish manuscripts that are valid, important, lively, well-written, and succinct. They should be of interest to a broad range of busy practitioners, students, researchers, and scholars who have a clinical orientation. The purpose of a paper or letter may be to alert, review, discuss—above all, to teach. Titles should be short and intriguing. Avoid jargon, the overuse of abbreviations and acronyms, sexist language, redundancies, or expendable words and phrases (see *AMA Manual of Style*, 8th Edition).

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine*, 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, that should be noted in the cover letter and a copy of that publication should be included.

Manuscripts should not exceed 3,000 words (15 double-spaced pages). Case Reports, Alerts, and Notices should not exceed 1,500 words. Lessons From the Practice should not exceed 1,000 words.

Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include an abstract of no more than 200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

Letters to the Editor will be published at the discretion of the Editors and may be edited for style and brevity. Those of a scientific nature may be subject to peer review. They should be double-spaced and no more than 500 words in length. Authors will be sent galley proofs before publication.

Letter of Transmittal

All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone number included.

A letter of transmittal, except for one accompanying a manuscript from US Government employees whose work was done as part of their official duties, must include a paragraph that transfers copyright: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to *The Western Journal of Medicine*, in the event that such work is published by the journal."

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Research or project support should be included as a footnote to the manuscript or the accompanying cover letter.

Manuscripts concerned with experimental investigation on human subjects must include in the text of the manuscript a statement that all subjects gave their informed consent and that approval of the appropriate ethics committee was obtained.

Acknowledgements

Acknowledgements will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper.

Preparation of Manuscripts

Everything, including references, tables, legends, and abstracts, **must be double-spaced.**

The original manuscript and two copies should be submitted on standard-sized heavy bond paper. Allow at least a 2.5 to 3.5 cm margin on both sides. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

All values should be in Système International (SI) units, with metric equivalents following in parentheses. Temperature readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given when first used.

Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints, with the figure number, author's name, and top of the photo indicated with a label on the back. Recognizable photos of patients should be masked, written permission for publication obtained from the patients, and copies included with the manuscript. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

All manuscripts will be subject to peer review to determine the originality, validity, and importance of content and conclusions. Reviewers' comments will be returned with rejected manuscripts at the discretion of the Editors. All reviewers will remain anonymous. Any conflict of interest, actual or potential, will have been revealed to the Editors.

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A form to order reprints will be sent to the author when the article is published.

References

All references should be cited in the text and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in *WJM* style per the examples given below.

(All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.)

Journal Articles

Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Jones JS, Anderson HW Jr, Johnson DW: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation; whether the communication was oral or written; and the date (month) and year.

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β-hemolytic streptococci).
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Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
• Discontinue Ceclor in the event of allergic reactions to it.
• Prolonged use may result in overgrowth of nonsusceptible organisms.
• Positive direct Coombs' tests have been reported during treatment with cephalosporins.
• Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
• Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
• Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
• Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of **serum-sickness-like** reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
• Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
• Gastrointestinal (mostly diarrhea): 2.5%
• Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
• As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
• Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
• Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

Abnormalities in laboratory results of uncertain etiology.
• Slight elevations in hepatic enzymes.
• Transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia.
• Rare reports of increased prothrombin time with or without clinical bleeding in patients receiving Ceclor and Coumadin concomitantly.
• Abnormal urinalysis; elevations in BUN or serum creatinine.
• Positive direct Coombs' test.
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(Continued from Page 30)

March 9-16—**Second Annual "Minding the Body, Mending the Mind: Influencing Health and Healing" Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**14th Annual Urology Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**13th Annual Sports Medicine Conference.** Rose Medical Center, Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**Computers in Medicine Conference**, Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 23-30—**14th Annual Cancer Treatment Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

IDAHO

February 27-March 2—**Sun Valley Program.** Pierce County Medical Society (Washington) College of Medical Education at Sun Valley. Wed-Sat. Contact: PCMS CME, 705 S 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 1-3—**Ada County Medical Society 32nd Annual Medical Winter Clinics—Yuppie Diseases—Ills and Ailments of a Generation.** Shore Lodge, McCall. Fri-Sun. 9 hrs. $100. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

May 13-15—**Idaho Academy of Family Physicians—43rd Annual Meeting.** The Coeur d'Alene, Coeur D'Alene. Mon-Wed. Contact: Mrs Irma Sparks, Exec Dir, IAFP, PO Box 175, Boise 83701.

July 25-27—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 19—**Personality Disorders.** University of New Mexico School of Nursing and Pharmacy Auditorium, Albuquerque. Sat. Contact: Marsha VerPloegh, Psychiatric Medical Association, PO Box 26666, Albuquerque 87125. (505) 291-5375.

February 4-8—**Controversies in Medicine**, Alta, Utah. Mon-Fri. Contact: Neil Kaminsky, MD, New Mexico Mid-Winter Study Group, 717 Encino Place, NE, Ste 9, Albuquerque 87102.

February 15-16—**Southwest Psychiatric Symposium on Substance Abuse.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

March 16—**AIDS Update**, University of New Mexico School of Nursing and Pharmacy Auditorium, Albuquerque. Sat. Contact: Marsha VerPloegh, Psychiatric Medical Association, PO Box 26666, Albuquerque 87125. (505) 291-5375.

May 9-10—**New Mexico Medical Society Annual Meeting.** Albuquerque. Thurs-Fri. Contact: Glenn Taylor, NMMS, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or 1 (800) 748-1596.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

January 15-19—**Arthroscopic Surgery 1991** (Sponsor: UUMC). Tues-Sat. Phoenix, Arizona. Contact: (801) 581-7602.

January 17-21—**Ethics and Health** (Sponsor: UUMC). Thurs-Mon. University of Utah, Olpin Union Building, Salt Lake City. Contact: (801) 581-8664.

January 25-27—**Laser Surgery—Laparoscopic Cholecystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.
DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.
HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.
PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.
UMA: Utah Medical Association, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.
UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

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February 1-3—**Pediatric Update** (Sponsor: UUMC). Fri-Sun. Jackson, Wyoming. Contact: (801) 581-7001.

February 4-8—**Surgical Pathology** (Sponsor: UUMC). Mon-Fri. Park City. Contact: K. Rassmussen, (801) 379-7178.

February 10-15—**Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Judy Gallegos, (801) 581-8188.

February 10-15—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: Midge Beckman, (801) 581-7480.

February 11-16—**Microsurgery Workshop** (Sponsor: UUMC). Mon-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

February 11-16—**Orbital & Craniofacial Surgery** (Sponsor: UUMC). Mon-Sat. Snowbird. Contact: (801) 581-8664.

February 11-17—**Family Practice Refresher Course** (Sponsor: UUMC). Mon-Sun. Salt Lake Hilton, Salt Lake City. Contact: K. Chisholm, (801) 581-7234.

February 15-19—**The 35th Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: V. Larsen, (801) 581-6393.

February 17-20—**The 32nd Annual Oh/Gyn Update** (Sponsor: UUMC). Sun-Wed. The Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 19-22—**1991 Winter Ski Meeting and Ophthalmology Update** (Sponsor: UOS). Tues-Fri. Olympus Hotel, Salt Lake City. Contact: UOS.

February 19-23—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sun. The Marriott Hotel, Salt Lake City. Contact: (801) 588-2000.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 17—**Law and Medicine Symposium.** Tacoma. Thurs. Contact: PCMS CME.

January 17—**Cancer Conference.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-5322.

January 19-20—**Advanced Cardiac Life Support Provider Course.** Seattle. Sat-Sun. Contact: VMMC.

January 23—**Pesticide Medicine.** Seattle. Wed. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 25-27—**Chest Conference: Lung Day XIX—1991 Annual Meeting.** Leavenworth. Tues-Thurs. Contact: American Thoracic Society, 1 (800) 732-9339.

February 8—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS, (206) 627-7137.

February 22-23—**Arthritis Update.** Seattle. Fri-Sat. Contact: U/W.

February 22-23—**Musculoskeletal Diseases for the Primary Care Physician.** Seattle. Fri-Sat. Contact: U/W.

February 28-March 1—**A Day in the Office: Common Problems in Pediatric Practice.** Seattle. Thurs-Fri. Contact: Group Health, (206) 326-3441.

March 1—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 1-2—**Psychiatric and Psychological Issues in Medical Practice.** Seattle. Fri-Sat. Contact: VMMC.

March 13-15—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

March 14-15—**Tacoma Academy of Internal Medicine.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 14-16—**Emergencies in Older Patients.** Seattle. Thurs-Sat. Contact: U/W.

March 15—**Inflammatory Bowel Disease.** Seattle. Fri. Contact: VMMC.

March 22-23—**Ophthalmology (WSAO)—Annual President's Meeting.** Seattle. Fri-Sat. Contact: (206) 441-9762.

April 2-5—**General Practice Review.** Scottsdale, Arizona. Tues-Fri. Contact: Pacific Northwest Educational Institute, (206) 258-6322.

April 3-4—**Cumulative Trauma Disorders of Upper Extremities.** Seattle. Sun-Mon. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 12-13—**Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS CME.

April 12-13—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 13-14—**Benton-Franklin County Medical Society Annual Meeting.** Tri-Cities. Sat-Sun. Contact: (509) 783-8616.

April 15-18—**The Best Approach 1991: Effective, Efficient Strategies in Cardiology, Orthopedics, Gastroenterology, and Pediatrics.** Kauai Sheraton, Hawaii. Fri-Mon. Contact: Group Health, (206) 326-3441.

April 15-26—**PM & R Review.** Seattle. Fri-Tues. Contact: U/W.

April 26-27—**Medical Issues of Active and Athletic Women.** Seattle. Fri-Sat. Contact: VMMC.

June 1—**Suhstance Ahuse.** Seattle. Sat. Contact: U/W.

June 21—**Horizons in Urology.** Seattle. Fri. Contact: U/W.

WYOMING

February 1-3—**Pediatric Update.** University of Utah School of Medicine at Jackson. Fri-Sun. Contact: UUMC, 50 N Medical Dr, Salt Lake City, UT 84132. (801) 581—2258.

June 13-15—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424 ◆

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RADIOLOGIST FOR SOUTHEASTERN UTAH. Excellent practice opportunity to join second Radiologist. Primary service area of 30,000 people with 88-bed community hospital. Nuclear, CT, mammography, ultrasound, and radiography. Contact Milton Bauermeister, MD, Castleview Hospital, Price, UT 84501; (801) 637-4800, ext 280 or (801) 472-5403.

MARYSVILLE (YUBA CITY). Primary care provider. Northern California primary care clinic. Three physicians, three physician assistants. No OB. No surgery. Near mountains, close to Sacramento, 2½ hours to Lake Tahoe and San Francisco. Salary $86,113 plus. Please contact Ed Allen, 938 14th St, Marysville, CA 95901; or call (916) 741-6244.

LOOKING FOR A PRIMARY CARE Internal Medicine Geriatric position with challenging and appreciative patients, quality associates, tolerable schedules in an attractive community? Send CV to Julie A. Prazich, MD, Medical Director, Sharp Senior HealthCare, 3545 Fourth Ave, San Diego, CA 92103.

BC/BE PEDIATRICIAN WANTED for semi-rural community 25 miles south of San Francisco to associate with five member Family Practice group. Send inquiry with CV to Lawrence Bruguera, MD, Coastside Medical Clinic, 225 S. Cabrillo Hwy, Ste 100-A, Half Moon Bay, CA 94019.

OPPORTUNITY for full- and part-time Emergency Physicians. Excellent fee-per-patient load ratio. Malpractice paid. Also, Emergency Department/Family Practice positions for urgent care/industrial center. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

BC/BE INTERNIST NEEDED. Opportunity to join part of a comprehensive medical group practice located in the suburbs of San Francisco. Professional setting of 36 physicians. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

BOARD CERTIFIED FAMILY PHYSICIAN wanted to join two others within larger multispecialty practice in Kauai. OB preferred. Send CV to Drs Clay and Ratliff at 4366 Kukui Grove St, Ste 201, Lihue, HI 96766; or call (808) 245-4600.

WARM AND SUNNY ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 145 plus physicians in 14 clinic locations throughout Arizona has positions available in Family Practice, Internal Medicine, Pediatrics, and Orthopedics. Exceptional fringe benefits, profit sharing, and retirement program. Guarantee for first two years, plus incentive. Early shareholder. Fee-for-service, as well as physician owned HMO. Must be BC/BE. Call or write Bill De Long at Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; 1 (800) 658-9166.

OB/GYN. BC/BE to join expanding multispecialty group practice as third Obstetrician. Competitive salary, benefit package with potential for partnership status. Desirable southwest metropolitan area. Send inquiries to Larry Levey, Administrator, Tucson Medical Associates, 116 N. Tucson Blvd, Tucson, AZ 85716; (602) 327-5531.

INTERNAL MEDICINE. BC/BE to join expanding multispecialty group practice. Competitive salary, benefit package with potential for partnership status. Desirable southwest metropolitan area. Send inquiries to Larry Levey, Administrator, Tucson Medical Associates, 116 N. Tucson Blvd, Tucson, AZ 85716; (602) 327-5531.

SOUTHERN CALIFORNIA NEUROSURGEONS

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for staff positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

PHYSICIANS WANTED

PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional BC/BE physicians in the following specialities:

- **NEUROLOGY.** Establish private practice with no investment, guaranteed income. Proficiency in EEG, EMG required.
- **GENERAL/THORACIC SURGERY.** Establish private practice in General and Thoracic Surgery (no open heart) with no investment, guaranteed income.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **ORTHOPEDIC SURGERY.** No investment, guaranteed income. Above average earning potential.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient. (California license is required.)
- **PEDIATRICIAN.** Join busy private Pediatric Practice. Attractive salary with arrangements for future association.
- **FAMILY PHYSICIAN.** Join busy four Family Practice group in private practice. Salary or guarantee first year.

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 90,000; a growing area with new businesses and a stable economy.

Located in central California near Sequoia National Park, Tulare offers an excellent family oriented lifestyle and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

Contact:

Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is searching for physicians residency trained or BC in Emergency Medicine. The Health Science Campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level One Trauma Center, has paramedic base station training responsibilities, and has a helicopter service. An approved Emergency Medicine Residency Program began in July 1990. Emergency Physicians supervise medical students, interns, and residents, in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive, and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

RADIOLOGIST—SAN FRANCISCO BAY AREA. Growing outpatient imaging practice with CT/MRI. Salary leading to partnership. Send CV to Murray Solomon, MD, 450 Sutter St, Ste 835, San Francisco, CA 94108; (415) 296-8654.

(Continued on Page 118)

AIM HIGH

BE AN AIR FORCE PHYSICIAN.

Become the dedicated physician you want to be while serving your country in today's Air Force. Discover the tremendous benefits of Air Force medicine. Talk to an Air Force medical program manager about the quality lifestyle, quality benefits and 30 days of vacation with pay per year that are part of a medical career with the Air Force. And enjoy the satisfaction of a general practice without the financial and management burden. Today's Air Force offers an exciting medical environment and a non-contributing retirement plan for physicians who qualify. Learn more about becoming an Air Force physician. Call

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AIR FORCE

(Continued from Page 116)

PHYSICIANS WANTED

EXCELLENT
FAMILY PRACTICE
OPPORTUNITY

ROCKWOOD CLINIC, P.S.—a network of Family Practice clinics (main building and six satellites) seeks BE/BC Family Practitioners to join these busy independent practices offering the full range of inpatient/outpatient services, including Obstetrics. ADVANTAGES INCLUDE:

- Join the largest department within this multispecialty group (15 Family Practitioners)
- Immediate in-house specialty consultation
- Well trained administrative support to assist in business matters, while allowing autonomy regarding the decisions of your practice
- Attractive benefit package includes excellent salary leading to early shareholder status

SPOKANE, WASHINGTON (metropolitan population 350,000) offers very affordable housing, unlimited year-round recreation, excellent schools, and numerous cultural organizations.

CONTACT:
Colleen Mooney
Recruitment Coordinator
Rockwood Clinic
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

CALIFORNIA MULTISPECIALTY. Dermatologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

PHYSICIANS WANTED

OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

RADIOLOGIST. Part-time position available immediately in small hospital with general Radiography and Fluoroscopy, Mammography, and Ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

OCCUPATIONAL MEDICINE PHYSICIAN. Modesto Occupational Medical Clinic is looking for a full-time physician. We are a young, thriving high-volume practice in need of an additional physician who is BC/BE or with experience in Occupational Medicine. We are a full service clinic with x-ray, Physical Therapy, and all equipment for Occupational Monitoring. We have a large client company base with several years of experience. This person must have good clinical skills, be highly motivated, be energetic, and looking for a challenging career. Position may include administrative and clinic responsibilities with opportunity for partnership. We are located in the central valley two hours from both San Francisco and several excellent ski resorts in the Sierra Nevada. Please contact Susan Hooper, 1600 Sunrise, Ste 16, Modesto, CA 95350; (209) 529-6234.

ORTHOPEDIC SURGEON. University of California, San Francisco seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position at the Valley Medical Center, Fresno. The Orthopedic Department at VMC supports a busy Trauma Service and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. This position also offers private practice opportunities in a setting within the faculty group. Competitive salary and benefits. The central California location offers affordable and enjoyable year-round recreational living. Address inquiries and CVs to H. B. Morgan, Jr, MD, Chief of Orthopedics, 2212 N Winery, #130, Fresno, CA 93703. EO/AA employer, women and minorities are encouraged to apply.

INTERNIST—SAN FRANCISCO. Full-time or part-time position available for Internist or Family Practitioner to practice in an innovative, nationally recognized HMO for frail elderly. Malpractice paid. Competitive salary and excellent benefits. Reply with CV to Catherine Eng, MD, On Lok Senior Health Services, 1441 Powell, San Francisco, CA 94133; (415) 989-2578. EOE.

FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

EmCare
GOVERNMENT SERVICES, INC.

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Qualified Physicians Being Recruited For Opportunities Offering

Competitive Guaranteed Income with Fee for Service Income Potential
Professional Liability Insurance
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For additional information on opportunities and locations contact

Glenn W. Farmer
Director
Catherine M. Dawson
Assistant Director

1-800-527-2145

EGSI, 1717 Main Street, Suite 5200
Dallas, Texas 75201
214/761-9200

PHYSICIANS WANTED

FAMILY PRACTITIONER
PEDIATRICIAN

Multispecialty group located in San Luis Obispo, California, seeks BC/BE physicians. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to:

Physician Recruitment
San Luis Medical Clinic
1235 Osos St
San Luis Obispo, CA 93401

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

PEDIATRICIAN BC/BE needed in northern suburb of San Francisco. Opportunity to join part of a multispecialty group. Applicant should demonstrate strong academic skills committed to quality personalized care. Forward CV to Peter Earley, Physician Relations, Ross Valley Medical Group, 2200 Larkspur Landing Circle, Ste 103, Larkspur, CA 94939.

GREAT OPPORTUNITIES IN NORTHERN CALIFORNIA. We are San Jose's leading multispecialty private group practice, and want a BC/BE physician with broadly based high level training to join our Department of Urgent Care and General Medicine. The position offers competitive salary plus incentive bonus, a comprehensive benefits package including retirement and 401K plan contributions, and early access to partnership and stockholder status. The south bay area provides a wide range of cultural and recreational activities, good schools, fine dining, and a congenial climate. We're growing, and we'd like to hear from you. Send your CV to Maureen Forrester, San Jose Medical Group, 45 S. 17th St, San Jose, CA 95112; or call us at (408) 282-7833.

OCCUPATIONAL MEDICINE—SAN FRANCISCO BAY AREA. Area's leading multispecialty private group practice is seeking a BC/BE primary care physician to join their expanding Department of Occupational Medicine. Range of practice includes pre-employment physicals, diagnostic evaluations, treatment of on-the-job injuries. If you are interested in building a career in Occupational Medicine, we will provide comprehensive training. Competitive salary, plus incentive, excellent benefits, paid malpractice. Located in the south bay which offers wonderful cultural/recreational activities, fine dining, outstanding climate and scenery, easy access to beach and mountains. For further information, please send CV or contact Maureen Forrester, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833.

OREGON. General Internal Medicine and Family Practice, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

SAN FRANCISCO. Primary Care Practice in Noe Valley seeks BC/BE Family Practitioner or Internist to join growing practice. Competitive salary, wonderful neighborhood, partnership option. Send résumé to Noe Valley Family Medicine, 3700 24th St, San Francisco, CA 94114.

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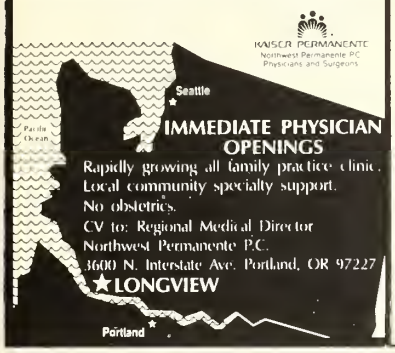
LONGVIEW, WASHINGTON



Longview is a picturesque, stable community of 42,000 located near the Columbia Gorge and the coastal mountains and beaches of Washington and Oregon. Members of our 12 physician group enjoy individual subpractices, infrequent call, and new state-of-the-art medical offices.

We invite you to contact us at the above address regarding practice opportunities. Or call Judy Parmenter, Physician Recruitment, (503) 280-2050 for further information.

BC/BE FAMILY PRACTITIONER to enjoy rural living with urban culture 20 minutes away. Generous vacation time to use the many nearby recreational opportunities. Join another Family Practitioner and two Physician Assistants in a Family Practice satellite of a large multispecialty clinic. Contact Jerry Corn, MD: (206) 687-5108 or Karen Stanton; (206) 254-1240.

NORTHERN CALIFORNIA—INTERNAL MEDICINE. The Permanente Medical Group is seeking a BC/BE Internist to join their thriving practice located in Redwood City. Critical care experience helpful but not crucial. We offer a highly competitive salary and a substantial benefits package which includes malpractice insurance, medical, dental and group life insurance, educational leave, an excellent retirement program and a desirable San Francisco bay area location. Please respond with CV to Norman Olson, MD, Chief, Department of Medicine, 1150 Veterans Blvd, Redwood City, CA 94603. EOE.

FAMILY PRACTICE, SAN DIEGO. Join a seven physician group—all Family Practice, great location. Good pay and benefits. No Obstetrics. Contact Andrea Bower, MD; (619) 745-2000, 815 E. Pennsylvania Ave, Escondido, CA 92025.

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy, urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, AD-WJM, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

TWO INTERNISTS seek an associate BE/BC Internist for busy Internal Medicine group practice located in a community of 60,000. Forty miles from San Francisco. Excellent modern hospital. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

A BE/BC NEPHROLOGIST is needed to join a two doctor practice in Nephrology forty miles from San Francisco. Excellent modern hospital with Chronic Dialysis unit next door. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

COASTAL CALIFORNIA 45,000 population. Well-trained 12 physician Primary Care group. Immediate/future need for Family Practice and Internal Medicine. Competitive salary and benefits with partnership after one year. On call schedule allows time for family and recreation. In Lompoc, you can do what you were trained to do, including OB, Pediatrics, and General Medicine. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

CHEYENNE, WYOMING. Immediate opening available for a dedicated, career oriented, full-time Emergency Physician with Urgent Care facility in Cheyenne, Wyoming. Competitive compensation plus malpractice insurance. Approximately 14 days per month, standard 12 hour shifts. Excellent living conditions, high quality school system, moderate taxes and living expenses, exciting recreational opportunities in the heart of the Rocky Mountain region. Call now for additional information or send CV to Janet Cowley, Recruitment Coordinator, PO Box 805, Cheyenne, WY 82003; (307) 632-1436, FAX (307) 635-4642.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Room Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

PHYSICIANS—PHOENIX, ARIZONA. Join six other physicians in providing comprehensive medical care for a 550-bed psychiatric hospital. Benefits include a generous pay schedule ($80,000 to $100,000 per year starting salary), regular daytime hours, no call or weekend duties, and an optional four-day work week. Interested applicants should send CV to Greg Maynard, MD, Director Medical Department, Arizona State Hospital, 2500 E. Van Buren, Phoenix, AZ 85008; or call (602) 244-1331.

EUGENE, OREGON. FAMILY PRACTICE. 36 physician multispecialty group is seeking BC/BE Family Physician. OB optional. Excellent schools. Abundant cultural and recreational opportunities. Near Cascade Mountains and coast. Home of University of Oregon. Please send CV to Rob Daugherty, MD, Oregon Medical Group, 2484 River Rd, Eugene, OR 97404; or phone (503) 688-9140.

BC/BE NORTHWESTERN CALIFORNIA. OB/GYN needed to join the oldest office in the Redwood area on the north coast. An excellent opportunity for a male or female American trained physician. Excellent compensation and incentive program leading to corporate membership in one year. Three physicians in office but only two doing obstetrics. Send CV and references to T. W. Loring, MD, 2607 Harris St, Ste E, Eureka, CA 95501; (707) 442-4593.

SAN FRANCISCO EAST BAY. BE/BC Internist needed to join ten physician Primary Care group practice in beautiful San Ramon Valley area. Excellent opportunity and compensation. Reply in confidence to Number 223, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CARDIOLOGIST—BC/BE sought to join a large hospital based multispecialty clinic. University affiliated residency program. Excellent fringe benefits. Competitive salary. California license required. Send CV to Aung-Win Chiong, MD, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825.

THE BEST OF BOTH WORLDS

Join our rapidly expanding and well established multi-specialty group practice in Southern California. It's the ideal environment for physicians who are seeking a small community atmosphere, combined with the latest medical resources and technology of a major force in the health care industry.

Immediate practice opportunities available for Physicians in the following specialties:

- ***Family Practice***
- ***Internal Medicine***
- ***Obstetrics/Gynecology***
- ***Pediatrics***
- ***Orthopedic Surgery***
- ***Otolaryngology***

We offer an excellent compensation and benefits package including ***professional liability coverage, life and disability insurance, medical/dental coverage, paid vacation, sick leave and paid educational time.***

For more information, send your CV to Box #217, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA. Excellent Ambulatory Care and Emergency Medicine positions for BC/BE physicians. Northern, southern and central locations. Stable contracts, high hourlies, attractive facilities, profit-sharing, paid malpractice, excellent benefits. Opportunity for growth and leadership. Join our partnership of established Ambulatory Care and Emergency Medicine Physicians. Contact John Gravette, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612-3027; (415) 835-7431 or, outside of California (800) 842-2619.

YELLOWSTONE NATIONAL PARK. Physician to cover Outpatient Clinic, Emergency Room, and Inpatient at Lake Hospital from Memorial Day to mid September 1991. Send CV to Yellowstone Park Medical Services, 707 Sheridan Ave, Cody, WY 82414; or call (307) 578-2461.

JUNIOR FACULTY INTERNIST. University of California, San Francisco, Valley Medical Center, Fresno Medical Education Program, Department of Family Physician seeks recent BE Internal Medicine graduate to attend on a general Internal Medicine ward, teach in the ambulatory setting, and contribute to the intellectual life of the Department. Our full-time experienced Senior Internist will provide faculty development, consultation, and backup. VMC is a major affiliate of UCSF School of Medicine sponsoring several well regarded programs, including Internal Medicine. Delightful and affordable central California location. Salary guarantee and faculty practice plan incentive. Available July 1, 1991. Send CV to Robert Heiligman, MD, Assistant Chief of Family Practice, 2212 N. Winery, #130, Fresno, CA 93703. EOE, women and minorities are encouraged to apply.

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PHYSICIANS WANTED

PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialities for hospitals, clinics, multi-specialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

PEDIATRICIAN, BC/BE to join group Family Practice/Pediatrics. Growing community with growing pediatric population. Active Nursery Level II hospital and nursery with NNP coverage. Offering competitive salary, equal call schedules, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

INTERNIST—PACIFIC NORTHWEST. Excellent opportunity for BC/BE Internist to join group of five Internists in suburban Idaho community. Near urban referral center with good subspecialty backup. Also near superb hunting, fishing, camping, and skiing. Please call or refer résumé to Susan Davis, Administrator, Caldwell Internal Medicine Professional Association, 222 E. Elm, Caldwell, ID 83605; 1 (208) 459-4667.

SEATTLE: BC/BE General Internist to join BC Internists' group with three Seattle area offices. No income guarantee; group and location excellent. Call or write Douglas Bovee, MD, 3203 W. McGraw, Seattle, WA 98199; (206) 285-3139.

SOUTHERN CALIFORNIA. 300-bed hospital in growth community at foothills of Mt Baldy. Opportunity for OB/GYN, Family Practice, and Rheumatologist to associate with successful practitioners. Hospital will provide generous guarantee, moving expenses, and practice management assistance. Please contact Ken Baker, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS. Opportunities available in Sacramento, San Jose, Salinas, Oakland, and San Diego for BC physicians in Dermatology, Internal Medicine, Orthopedics, Ophthalmology, Otolaryngology, Psychiatry, Toxicology, and Neurology with a multispecialty medical group which provides forensic medical evaluations. This is an excellent opportunity to supplement income as well as associate with a well respected medical group whose practice is limited to evaluations. Send inquiry and CV to Terence Doyle, Disability Reporters, 696 E. Santa Clara St, Ste 105, San Jose, CA 95112; (408) 283-8689.

23 PHYSICIAN GROUP PRACTICE. Recent population growth and demand have created the need for several specialists including OB/GYN, Family Practice, Internal Medicine, Cardiology, and Pediatrics in this 23 physician group practice. Situated 60 miles east of San Francisco, the group serves a local population of 35,000. Nearby skiing and boating, reasonable housing, and an excellent school system. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

SOUTHERN CALIFORNIA

Upscale, family oriented community in the eastern foothills of Los Angeles County offers qualified primary care physicians (Family Practice, General Internist, Pediatricians) both group and private practice opportunities. Complete compensation package includes salary guarantees, practice management and marketing support, malpractice, and relocation expense reimbursement. BC/BE. Excellent growth potential. Send CV to Gary May, Foothill Presbyterian Hospital, 250 S. Grand Ave, Glendora, CA 91740; or call (818) 963-8411.

PHYSICIANS WANTED

SOUTHERN CALIFORNIA HEAD AND NECK SURGEONS

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for both staff and chief positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

CENTRAL CALIFORNIA. Hospital based teaching opportunity for OB/GYN in a new residency program at the KMC. Ideal candidate is a team player with a strong desire to teach residents. This UCLA affiliate has a busy OB department with 5,000 deliveries per year. Please contact Mary Letterii, Vice President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

CENTRAL CALIFORNIA. Anesthesiologist Medical Director needed for high volume teaching hospital. Opportunity to develop contract for services with Kern County. Successful candidate has good track record of leadership with solid clinical background. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

MEDICAL DIRECTOR TRAUMA SERVICES. Eden Hospital. Level II Regional Trauma Center, Alameda county. Available December 1, 1990. Submit CV to Trauma Services, Eden Hospital, 20103 Lake Chabot Rd, Castro Valley, CA 94546; or call Dr Peter Wong, (415) 886-0535 or Dr Brian Walker, (415) 881-8445.

PRIMARY CARE PHYSICIAN wanted for expanding eastern Washington clinic. Full- and part-time positions available. Located in prime recreational area. Skiing, sailing, fishing, hunting all within a short distance. Enjoy mild climate, excellent schools and a major university branch campus in growing community of 100,000 plus. Challenging work in a superbly equipped clinic with state-of-the-art lab, x-ray, laser, and endoscopy. Above average compensation and benefits including malpractice, health insurance, and CME. Contact Dr Stephen Smith, (509) 545-8340 or fax (509) 545-1136.

INTERNIST BC/BE. Current associate leaving for academic position. Busy Internal Medicine practice available July 1991. Currently netting $155K, on call every seventh weekend. If you desire to enjoy life while maintaining a fully established and challenging practice send CV to Cecil Bullard, MD, 5339 N. Fresno, #107D, Fresno, CA 93710.

CALIFORNIA
FAMILY PRACTICE
INTERNAL MEDICINE
SURGEON and PEDIATRIC

physicians to join Family Walk-In Medical Centers staff, a growing health care provider with five medical centers in Fresno, California, which is located in the Central San Joaquin Valley. Fresno metropolitan area has a population of over 400,000. Easy access to major metropolitan areas, Pacific coast and the Sierras. Salary guarantee of $100K to $120K for Family Practice, Internal Medicine, and Pediatric physicians; $150K for Surgeons, or equal to an average of the last two years' earnings, whichever is greater. Malpractice paid. Excellent working conditions. Contact:

D. Duane Oswald
Family Walk-In Medical Centers
PO Box 27680
Fresno, CA 93729-7680

PHYSICIANS WANTED

HEMATOLOGIST
ONCOLOGIST
ENDOCRINOLOGIST
NEUROLOGIST

Multispecialty group practice located in the Puget Sound area. Please send CV with reply to:

Number 212
Western Journal of Medicine
PO Box 7602
San Francisco, CA 94120-7602

FAMILY PRACTICE—FRESNO. Family Practice, Emergency Room, Occupational Medicine Physician BC/BE to join expanding group to provide Family Medicine, Occupational Medicine, and Urgent Care Medicine in a well equipped clinic setting. Competitive salary with incentive plan, paid malpractice. Send CV to Medical Director, 3636 N. First St, Ste 162, Fresno, CA 93726; (209) 221-2022.

BC/BE INTERNIST needed to share practice/call with three others in busy and attractive community. Cody, Wyoming is located only 50 miles from Yellowstone National Park. Area abundant in fishing, hunting, and outdoor sports. No state income tax! 181-bed multi-service facility which includes Acute, Long Term Care, and Chemical Dependency Center. For more information call Ruth McDaniel, CEO at (307) 578-2488 or send CV to West Park Hospital, 707 Sheridan Ave, Cody, WY 82414. EOE.

TUCSON, ARIZONA
FAMILY PRACTICE

An immediate need exists to join this busy Family Practice adjacent to Northwest Hospital in the newly completed medical office building. Call and coverage is one to five. A generous salary, plus bonus and expenses, is provided. Should you require additional information, please call:

Herbert Jalowsky, MD
(602) 742-0414

or forward your CV to:

1925 W. Orange Grove Rd
#105
Tucson, AZ 85701

(Continued on Page 121)

THE PERMANENTE MEDICAL GROUP NORTHERN CALIFORNIA

QUALITY

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LEADERSHIP

GROWTH

SUPPORT

REWARDS

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7153, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

KAISER PERMANENTE
Good People. Good Medicine.

(Continued from Page 120)

PHYSICIANS WANTED

PRIMARY CARE IN MENDOCINO COUNTY
Part-time physician needed to join outstanding staff of rural health center in beautiful Mendocino County north of San Francisco, near coast. Competitive salary. Pay for travel time negotiable. No OB or night call. Potential for full-time work in future. Family Practice preferred. CV to **Charles White, MD, Long Valley Health Center, PO Box 870, Laytonville, CA 95454; (707) 984-6131.**

PRACTICE OPPORTUNITIES. Family Practice, Internal Medicine, and Obstetrics and Gynecology positions available in San Diego, California; Phoenix, Arizona; Seattle, Washington; and Salt Lake City, Utah. Contact Eric Bennett, PO Box 5316, Scottsdale, AZ 85261; (602) 998-4540.

WE SEEK PRIMARY CARE PHYSICIANS for challenging career opportunities. Register by sending CV or call in confidence to Annashae Corporation, 230 Alpha Park, Cleveland, OH 44143-2202; 1 (800) 245-2662. EEC/MF.

UNIQUE CLINICAL INTERNAL MEDICINE FELLOWSHIP. UCLA Department of Medicine offering fourth year training in Internal Medicine, through the Kennamer Fellowship, supported by the Albert Parvin Foundation. Fellowship begins July 1, 1992 for candidates BC/BE in Internal Medicine. A one year fellowship for practice careers. One fellow will be based at each of UCLA's major affiliates: Cedars-Sinai, Harbor, UCLA-San Fernando Valley, UCLA and Wadsworth/VA. Stipend is $33,500 plus the benefits program available at base hospital you choose. For forms and details write Roy T. Young, MD, UCLA Department of Medicine, 32-115 CHS, 10833 Le Conte Blvd, Los Angeles, CA 90024. Applications deadline April 30, 1991. Interviews by invitation. All applicants notified before July 1, 1991. Equal Opportunity/Affirmative Action Employer.

SAN FRANCISCO BAY AREA BC/BE INTERNISTS
We are currently seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 pre-paid health plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city, and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to:

Winslow Wong, MD
Attn: Administration
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545
EOE

WASHINGTON, PUGET SOUND. Part- or full-time Emergency Department practice with low volume, excellent medical staff, and great freedom of scheduling. Malpractice paid. Independent contractor. Send CV to TECP, 955 Tacoma Ave S., Ste 210, Tacoma, WA 98402.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

CALIFORNIA
Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (415) 601-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

BC/BE FAMILY PRACTITIONER, OB-competent, for nonprofit community clinic in California redwood country. Rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

COLORADO. BC/BE INTERNIST to join three Internists in multispecialty group. Excellent opportunity for person interested in rural living, mountain recreation, and health care for medically underserved population. Send CV to Marguerite Salazar, 204 Carson Ave, Alamosa, CO 81101; (719) 589-5161.

SAN JOAQUIN VALLEY. Excellent opportunity for Family Practitioner to serve the underserved. No night call or weekends. Competitive salary plus benefits, paid malpractice. Agricultural community, one hour from the mountains, two hours from the coast. Bilingual English-Spanish helpful. Send CV to Hugh F. Stallworth, MD, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

NEPHROLOGY—LAS VEGAS, NEVADA. Established group is seeking an additional Nephrologist for private practice. For details, call Eloise Gusman; toll-free, 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

(Continued on Page 122)

(Continued from Page 121)

KAISER PERMANENTE

Good People Good Medicine

NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

PHYSICIAN, NORTHERN ARIZONA UNIVERSITY. Progressive, accredited student health center is seeking a 12 month physician to provide high quality Primary Care to a student population of 14,500. Fronske Health Center is a modern, fully equipped facility with a staff of seven practitioners. Northern Arizona University is situated in beautiful, mountainous, Flagstaff, Arizona. It is a summer/winter recreation area with skiing, hiking, camping, fishing, and boating. Position begins August 1991. Please address inquiries to Leonard A. Wright, MD, Director, PO Box 6033, Flagstaff, AZ 86011. NAU is an AA/EOE. Women and minority applicants are encouraged to apply.

EMERGENCY PHYSICIAN. Immediate opening; competitive salary, occurrence insurance. New facility, low volume Emergency Department. Rural location, excellent outdoor recreation; hunting, fishing, hiking, skiing. ACLS/ATLS required. Send CV to Steven P. French, MD, 190 Arrowhead, Evanston, WY; or call (307) 789-3636.

INTERNAL MEDICINE. Inviting BC/BE Internist to associate with well established BC Internist in rural Alaska. Excellent hospital and medical staff support. Beautiful area with mild climate and easy access to urban activities in nearby Anchorage. First year negotiable (salary with incentives and benefits) and subsequent joint corporation. Please call (907) 745-8432.

MEDICAL DIRECTOR. Family Practice Physician (BC/BE) for community based clinic. Emphasis Family Planning, Primary Care, Pediatrics, STD and health education. Responsibile for medical policy, QA, and supervision of clinical staff. Bilingual/cultural Hispanic preferred. Inquiries to EVCC, 2470 Alvin Ave, #3, San Jose, CA 95121. EOE.

GREATER SEATTLE. BC/BE General Internist needed to join busy, office-based Primary Care Practice 30 minutes north of Seattle. Quality of life superb with weekend call one in six and unlimited recreational opportunities within minutes. Financial potential excellent. Prefer full-time but will consider part-time to start. Reply to Number 229, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602 with CV and cover letter. Interview expenses will be paid.

CALIFORNIA

Immediate permanent placement opportunities in Internal Medicine, Plastic Surgery, Urgent Care, Pediatrics, Otolaryngology, General Surgery with Trauma and Family Practice. For information call/send CV to **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

WASHINGTON STATE

ROCKWOOD CLINIC, PS

An expanding 70 physician multispecialty fee-for-service group seeks BC/BE physicians in the following specialties:

ALLERGY	FAMILY PRACTICE
CARDIOLOGY	OCCUPATIONAL MEDICINE
DERMATOLOGY	HEMATOLOGY/ONCOLOGY
INTERNAL MEDICINE	NEPHROLOGY
PEDIATRICS	RHEUMATOLOGY
URGENT CARE CENTER—	ORTHOPEDICS

seeks Emergency Medicine and Family Practice Physicians (BC/BE).

Attractive benefit package includes competitive salary leading to early shareholder status.

CONTACT: **Colleen Mooney, Recruitment Coordinator**
Rockwood Clinic, PS
E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

COME ENJOY SPOKANE'S QUALITY LIFE-STYLE!

CALIFORNIA, BERKELEY. Experienced Emergency Room, Family Practice, Internal Medicine, and Urgent Care Physicians sought to staff an inpatient service at a large community hospital. Excellent hours (no nights) and compensation. Applicants must be BC/BE in either Emergency Medicine, Family Practice, or Internal Medicine. Job parameters may be configured to accommodate full- or half-time commitments. Please send CV to Joan Wendell, Office Manager, PO Box 5138, Berkeley, CA 94705.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

RADIOLOGIST NEEDED to join one other in a 60-bed hospital based practice with GE 1.5 MRI, 9800 CT, Doppler US, SPECT nuclear, angiography. Excellent salary leading to early partnership. Unique opportunity to join a sophisticated practice while living among the redwoods in a northern California coastal city with a referral population of over 100,000. Send CV to Dr Jackson, 3560 N St, Eureka, CA 95501; (707) 445-5993.

INTERNAL MEDICINE PRACTICE. Seek American trained, BC Internist to time share, for time control and quality medicine. Excellent hospital facilities and medical staff. Outstanding living area. Contact S. Johnson, MD, 721 Sheridan Ave, Cody, WY 82414; (307) 527-6415.

SOUTHERN CALIFORNIA—CLINICAL ALLERGISTS/IMMUNOLOGISTS AND PEDIATRIC PULMONOLOGIST

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for staff positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through 1993. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD. EOE/M/F/V/H.

ENDOCRINOLOGY—LAS VEGAS AND RENO/SPARKS, NEVADA AND WEST PALM BEACH, FLORIDA! Established groups are seeking additional Endocrinologists for private practice. For details, call Eloise Gusman; toll-free 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

MEMORIAL CLINIC offers excellent opportunity for BC/BE Family Practitioner to establish a second Family Practice neighborhood clinic. OB optional. Competitive salary and excellent benefits. Send CV to Memorial Clinic, Attention Inge Hart, 500 Lilly Rd, N.E., Olympia, WA 98506; (206) 456-1122, ext 249.

PHYSICIAN

Los Angeles County, Department of Health Services, is seeking full-time or certified physicians in obstetrics and gynecology. Competitive salaries, excellent benefits and malpractice insurance. Send C.V. to: **METRO WEST, Mary Abbott, M.D., H. CLAUDE HUDSON COMPREHENSIVE HEALTH CENTER, 2829 S. Grand Avenue, Los Angeles, CA 90007, (213) 744-3750.** Equal Opportunity Employer M/F.

(Continued on Page 123)

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PHYSICIANS WANTED

ORTHOPEDIC SURGEON

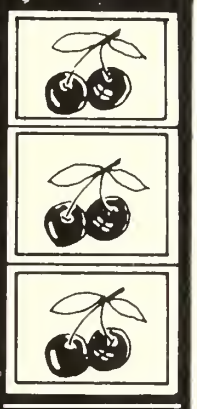
BC Orthopedic Surgeon needed for office practice in beautiful southern California area. Full- or part-time, surgery optional. Excellent compensation package. Send CV to **Ronald Gilbert, MD, c/o Gilbert Medical Group, 1076 E. First St, #A, Tustin, CA 92680; or call (714) 832-1516.**

DENVER—FAMILY PHYSICIANS. Opportunities now exist for Family Physicians in the Denver suburbs of Aurora and Thornton. Several solo Family Practitioners and groups, including MDs and DOs, are now seeking additional members. For more information, send your CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-1A, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

MEDICAL DIRECTOR. Opportunity to shape newly formed community health center practice. BC/BE Family Practice, Internal Medicine, OB/GYN, Pediatrician, experienced in clinical management of all age groups. Multi-ethnic medically indigent population expected. Send résumé to Luisa Buada, Executive Director, Berkeley Primary Care Access Clinic, Inc, PO Box 11406, Berkeley, CA 94701-2406; (415) 540-4536.

OBSTETRICS/PEDIATRICS. Small multispecialty group seeks second Pediatrician and OB/GYN to work with present physicians. Excellent compensation and benefits. Looking for long-term partnership. Call or send CV to Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

ADS GET RESULTS



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In addition to Southern California's year 'round wonderful weather, you'll find a well-rounded professional career with FHP, one of America's most successful HMOs.

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And with predictable hours, 3 weeks paid vacation and paid holidays, you'll have time to enjoy the unique lifestyle of our Southern California locations.

Call us at 800-336-2255 (in CA) or 800-446-2255 (outside CA) or send your resume/CV to: **FHP Professional Staffing, Dept. 99, 9900 Talbert Ave., Fountain Valley, CA 92708.** Equal Opportunity Employer.

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FHP® HEALTH CARE

(Continued on Page 124)

The benefits of group practice.

Physicians who want to enjoy the advantages of group practice without an administrative burden will really appreciate CIGNA Healthplan.

As a participating physician at one of our Staff Model health care centers, you'll join a team of equally dedicated physicians practicing within a consultative environment. But, unlike a group practice, your administrative work is carefully orchestrated by a competent staff of CIGNA Healthplan employees, enabling you to focus on patient care.

Currently, we have practice opportunities available for:

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- Anesthesiologist
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  - Medicine
  - Oncology
- Dermatologist
- Family Physician
- Gastroenterologist
- General Internist
- Invasive Cardiologist
- Nephrologist
- Obstetrician/Gynecologist
- Orthopedics
- Otolaryngologist
- Pathologist
- Pediatrician
- Pulmonologist

ARIZONA

Phoenix

- Family Physicians
- Internists
- Obstetricians/Gynecologists
- Orthopedics
- Pediatricians
- Radiology
- Urgent Care

As one of the nation's oldest and largest managed health care companies, CIGNA Healthplan understands the environment and resources physicians need to practice quality care.

We offer a competitive compensation and benefits package, paid malpractice insurance and continuing medical education. To receive more information about becoming a CIGNA Healthplan physician, please call or send your CV to one of the addresses listed below:

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Suite 400-49
Glendale, CA 91203
800-468-9013

Arizona
CIGNA Healthplan
Professional Staffing
Dept. 49
P.O. Box 16145
Phoenix, AZ 85011-6145
800-252-2471

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(Continued from Page 123)

PHYSICIANS WANTED

ReadiCare, Inc

ReadiCare currently has numerous opportunities in California and Washington state for qualified physicians. We offer:

- Flexible hours and days
- No on-call or mandatory weekends
- Competitive salary plus bonus plan
- Paid vacation, sick holiday and CME
- 401(k) Plan
- Full medical/dental
- Relocation assistance

Contact:

Marilyn Burke
(800) 237-3234
ReadiCare, Inc
PO Box 2457
Santa Clara, CA 95055

WASHINGTON—PUGET SOUND. Semi-rural clinic needs Primary Care physician, Internist, or Family Physician. Part-time or possibly full-time. Fully equipped facility, close to Olympia and Tacoma, active practice, no Obstetrics. Send CV and references to Karl Champion, PO Box 760, Yelm, WA 98597.

CALIFORNIA—NAPA. Attention General Practitioners, Family Practitioners, Internists, Emergency Room Physicians: Napa State Hospital has two full-time positions for medical/surgical on-duty coverage, 4:30 pm to 8:30 am (16 hour shift, ten days per month). No responsibility for psychiatric call. Salary $77,472 to $85,224 annually, with raise on January 1, 1991. Benefit package approximately 33% additionally. Napa State Hospital has a large (100 plus) well trained medical staff, intensive on-campus CME, and a university affiliated research unit. EOE, Affirmative Action, physicians union. Send CV to Jeffrey Zwerin, DO, Medical Director, Napa State Hospital, 2100 Napa-Vallejo Hwy, Napa, CA 94558-6293; telephone (707) 253-5434. In California; 1 (800) 421-0666.

FAMILY PRACTICE-HOSPITAL SPONSORED CLINIC OPPORTUNITY. Dynamic, growth oriented hospital in beautiful north central Wisconsin is seeking Family Physicians to respond to growing community demand. The administrative burdens of medical practice will be minimized in this hospital managed clinic. The hospital has committed to an income and benefit package which is significantly higher than similar opportunities. Package includes base income, incentive bonus, malpractice, disability, signing bonus and student loan reduction/forgiveness program. All relocation costs will be borne by the hospital. Please contact Kari Wangsness, Associate, The Chancellor Group, Inc, France Place, Ste 920, 3601 Minnesota Dr, Bloomington, MN 55435; (612) 835-5123.

PHYSICIANS WANTED

OTOLARYNGOLOGIST WANTED

Two doctor ENT office. Senior member retiring in July of 1991. BC/BE.

Needed in growth area of beautiful northern California.

Allergy and head and neck surgery also provided, as well as Audiology services in office.

Please send your CV with references to:

David L. Williams, MD
3330 Churn Creek Rd, D5
Redding, CA 96002.

Area brochure available upon request.

THE VA MEDICAL CENTER AT PRESCOTT, ARIZONA is recruiting for a physician experienced in a general medical practice who is BC/BE in any of various specialties, who has clinical knowledge of alcoholism, and desire, interest, or experience in administration to be the clinical director of a 208-bed domiciliary care program. Four major programs are currently in place: (a) care for veterans no longer capable of independent living, (b) care for homeless veterans, (c) vocational rehabilitation training and placement, (d) post alcohol/drug recovery treatment care. The Medical Center is a 150-bed general medical and 60-bed nursing home facility with a staff of approximately 650 employees. It is situated on the grounds of historic Fort Whipple. Prescott is a community of 25,000 set in the ponderosa pine foothills of the Bradshaw Range of the Rocky Mountains. At an elevation of 5,400 feet, the climate is temperate with occasional overnight snows in winter and summer highs in the 90s. Outdoor recreation and sports abound—year-round tennis and golf, 100 miles to big mountain skiing, fishing, sailing, boating on beautiful Lake Mead and Lake Powell. 200 miles to the excitement and night life of Las Vegas. All this in a quiet tree-lined community with 54 churches, a full service regional medical center, three colleges, six libraries, an excellent school system, a negligible crime rate, no pollution, low taxes, and reasonable housing prices. If you are interested in joining us in this idyllic life style and posses the requisite skill and absolutely spotless professional or employment history, then contact Sharon K. Harmeson at (602) 445-4860, ext 254, VAMC, Prescott, AZ 86313. An Equal Opportunity Employer.

GENERAL INTERNIST IN THE PACIFIC NORTHWEST. Busy 30 doctor multispecialty group practice looking for General Internist with ICU skills and interests to join an existing Internal Medicine department. Competitive salary and benefits; ownership status available after 18 months of employment. Send CV to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

WASHINGTON, PUGET SOUND. Full- or part-time position with expanding physician owned group. Well established, practicing adult Emergency Medicine. High level of Critical Care with excellent medical staff. Great flexibility in scheduling to enjoy the northwest. Partnership potential. Malpractice paid. ABEM certification or preparation required. Send CV to TECP, 955 Tacoma Ave S., Ste 210, Tacoma, WA 98402; (206) 627-2303.

SOUTHERN CALIFORNIA EMERGENCY PHYSICIANS

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for staff positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

PHYSICIANS WANTED

San Luis Obispo, California
Internal Medicine BC/BE

Immediate position available!
Join our busy multispeciality group located just 8 miles from the beach, halfway between SF and LA, and recently rated the "best small town in the USA".

A rewarding hospital based practice with:

- Guaranteed salary leading to percentage of billing
- Malpractice covered
- Excellent call rotation

Call or send CV to:
Fran Wolke
Director of Ambulatory Care
San Luis Obispo General Hospital
P.O. Box 8113
San Luis Obispo, CA 93403-8113

(805) 549-4936

DON'T FORGET!

The deadline for submitting classifieds for the March issue of WJM is January 25. Send your advertisement to:

Classified Advertising
WJM, PO Box 7602
San Francisco, CA
94120-7602
(415) 882-3376

(Continued on Page 125)

(Continued from Page 124)

PHYSICIANS WANTED

Salt Lake Clinic

333 S. 900 East, Salt Lake City, UT 84102

Salt Lake Clinic is seeking qualified candidates in:

- Obstetrics/Gynecology
- Neurology
- General Internal Medicine
- Nephrology

The Salt Lake Clinic celebrated its 75th anniversary in 1990, and is committed to providing high-quality medical care at a reasonable price. The clinic and its six satellite offices, all located in the Salt Lake Valley, are near an abundance of family oriented neighborhoods, schools, churches, and cultural and recreational opportunities. The community supports a symphony, ballet, professional sporting events, and seven different ski resorts within 45 minutes of the city. Please submit CV to Jane Renwick, medical staff secretary; or call (801) 535-8319.

INTERNAL MEDICINE. Full-time BC/BE Internist for multispeciality group in southeast Los Angeles. Office/hospital and consulting practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for partnership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

FAMILY PRACTITIONER. Full-time, BC/BE for growing multispecialty medical group in southeast Los Angeles. Some Spanish helpful. Top salary, benefits, and malpractice. Partnership potential second year. Send CV or call Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

SEATTLE, Washington suburban 26 physician primary care group has immediate need for Family Physicians and Internists. Area growth has created the need for a team physician who enjoys work as well as play in the beautiful (and affordable) Pacific northwest. Remuneration includes salary, bonus, and fringe benefit package. For more information, please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

EMERGENCY MEDICINE. Emergency Medicine group seeking career oriented ACLS, ATLS certified physician for an immediate opening. Moderate volume; income $140,000 plus. Great outdoor activities including hunting, fishing, boating, skiing, sailing, camping, and hiking in south central Washington on the Columbia River. Send CV to Kennewick Emergency Physicians, PS, PO Box 6192, Kennewick, WA 99336-6192; or call (509) 627-1798.

PRACTICE AVAILABLE

NORTHERN AND CENTRAL CALIFORNIA

Established practices available: Internal Medicine, Psychiatry, Pediatrics, Family Practice, GYN and Personal Injury. Reasonable terms and prices. Call/write to **Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, FAX (415) 376-0813.**

FAMILY PRACTICE FOR SALE. Established 30 years solo Family Practice fully equipped and furnished. Well rounded practice, block from hospital, teaching hospital six miles away. Excellent location, growing area 65 miles north of San Francisco in Wine Country. Share call five weekdays and one weekend per month. Available to stay to introduce new physician. Financing available. Please contact Richard C. Barnett, MD, 9323 Lakewood Dr, Windsor, CA 95492; or call (707) 838-3383.

FAMILY PRACTICE IN SPRING VALLEY, CALIFORNIA. Gross 180K, good location, well equipped office with 4,000 active patients. For complete information call San Diego's professional practice sales specialists (619) 283-7009.

PRACTICES AVAILABLE

SAN DIEGO COUNTY. Family, Internal, OB/GYN and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

COLORADO COLLEGE TOWN. General Internal Medicine and Geriatric practice and building for sale. $250,000, variable terms. Solo corporation. Great place to live. Call 1 (303) 482-4510 evenings.

PRACTICE FOR SALE in beautiful southwest Montana. Boating, fishing, camping, hunting, and skiing at your doorstep. Family Practice with terminations of pregnancy. Price: $50,000, negotiable. Reply to Number 224, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PUGET SOUND AREA (south of Tacoma). Purchase active Family Practice with over $325,000 gross. No OB. 1/5 weekend call coverage. Shared office with one Family Practitioner. Fully equipped with x-ray and laboratory. Number 226, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA. Family Practice established 1978. Gross 350K plus. Must sell for health reasons. Well equipped, good shared call schedule. No OB, no medical, minimal night call. Asking $52,000. May purchase over time or may lease. Reply to Number 227, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNAL MEDICINE PRACTICES FOR SALE. Practices available in southern California, both north and south of Los Angeles. For details, call Eloise Gusman; 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

FOR SALE. Established, busy Urology practice in southwestern New Mexico. No investment required. Excellent year 'round climate and outdoor recreational opportunities. Call collect, Pierson Deming, MD, (505) 388-1561 (office) or (505) 388-4557 (home): or call Steve Jacobson, Administrator, Gila Regional Medical Center, (505) 388-1591.

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To make arrangements for the program, potential facilitators should contact **Teri Stoeber in CMA's Department of Physician Education at (415) 882-5186.**

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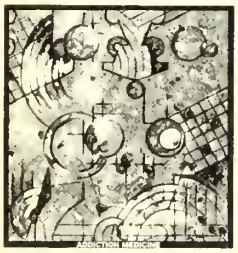

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 6-8, 1991, Loews Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 8-13, 1991, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 20-22, 1991, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1991, date and location to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1991, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1991, date and location to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1991, Quail Lodge, Carmel, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-10, 1991, The Marshall Building, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): April 26-28, 1991, Salisham.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1991, date and location to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1991, date and location to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 13-15, 1991, Jackson Lake Lodge, Moran.

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(ranitidine hydrochloride)

Zantac® 300 Tablets
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(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

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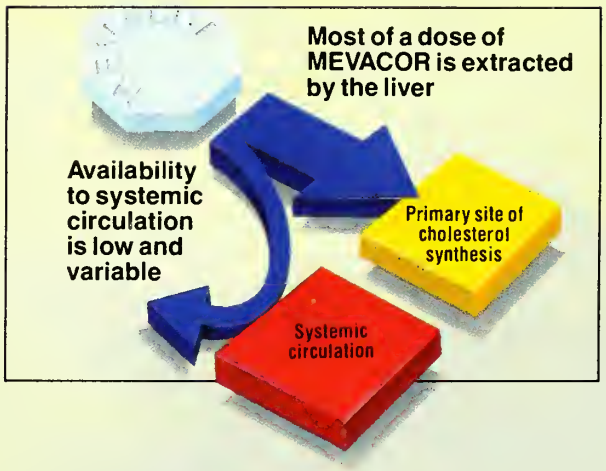

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In clinical studies, marked persistent increases (to more than three times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year. It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy, and periodically thereafter in all patients.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and slit-lamp monitoring, please refer to the Prescribing Information.

For a Brief Summary of Prescribing Information, please see the back of this advertisement.

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Pregnancy and lactation

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction*: **Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS).** When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Several cases of rhabdomyolysis have been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥ 1 g/day) of nicotinic acid. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness, or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy, the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General*: Before instituting therapy with MEVACOR® (Lovastatin, MSD), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Eye: There was a high prevalence of baseline lenticular opacities in the patient population included in the clinical trials with lovastatin. During these trials the appearance of new opacities was noted. The causal relationship of lovastatin to these findings has not been established.

Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase. There was no clinically significant change in visual acuity in the patients who had new opacities reported, nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity. Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastatin therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin*: See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (1.2 5 and 6.2 5 times the maximum recommended human dose).

A statistically significant increase ($p \leq 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose). No similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (1.2 5 or 6.2 5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (6.2 5 and 31.2 times the maximum recommended human dose), no increase was seen at a dosage of 20 mg/kg/day (1.2 5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region. acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat, however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (31.2 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (11.2 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadjusted $p = 0.025$). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose ~about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers: Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin, MSD) is generally well tolerated, adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR, about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences: Adverse experiences reported in patients treated with MEVACOR in controlled clinical studies are shown in the table below.

	MEVACOR (N = 613) %	Placebo (N = 82) %	Cholestyramine (N = 88) %	Probucol (N = 97) %
Gastrointestinal				
Constipation	4.9	—	34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9	—	13.6	3.1
Flatus	6.4	2.4	21.6	2.1
Abdominal pain/cramps	5.7	2.4	5.7	5.2
Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1.0
Headache	9.3	4.9	4.5	8.2
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	3.1
Dysgeusia	0.8	—	1.1	—

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9% and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

Uncontrolled Clinical Studies: The adverse experiences observed in uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function tests were observed at a higher incidence than in the controlled studies (see WARNINGS, *Liver Dysfunction*). Myopathy (myalgia with marked CPK elevations) was reported in approximately 0.5% of patients (see WARNINGS, *Skeletal Muscle*).

Causal Relationship Unclear: *Nervous System*: Peripheral neuropathy has been reported, the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

Special Senses: Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase (see PRECAUTIONS).

Post-marketing Experience: Additional adverse experiences occurring since the drug was marketed are listed below.

Clinical Adverse Experiences

Gastrointestinal: Hepatitis, cholestatic jaundice, anorexia, vomiting.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, flushing, malaise, and dyspnea.

Nervous System/Psychiatric: Psychic disturbances, including anxiety, paresthesia.

Skin: Erythema multiforme, including Stevens-Johnson syndrome, toxic epidermal necrolysis.

Causal Relationship Unknown

Gastrointestinal: Pancreatitis, stomatitis.

Skin: Alopecia.

Nervous System/Psychiatric: Depression, insomnia.

Metabolic: Edema.

Clinical Laboratory Test Findings

Liver Function Tests: Liver function test abnormalities, including elevated alkaline phosphatase and bilirubin.

Thyroid Function Tests: Rare reports of thyroid function test abnormalities in patients taking concomitant thyroxine.

OVERDOSAGE: The oral LD_{50} of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses, the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* for dose response results).

For those patients with severely elevated serum cholesterol levels (i.e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at 40 mg/day.

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), the maximum recommended dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

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For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J0MC48R (510)

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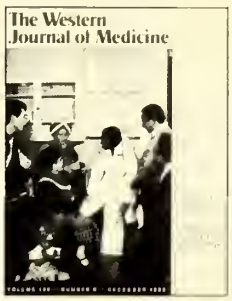
Women and Medicine

This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

Cross-cultural Medicine



Cross-cultural medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

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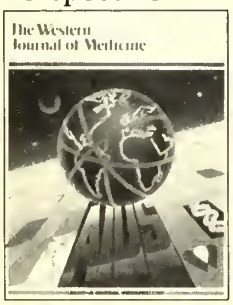

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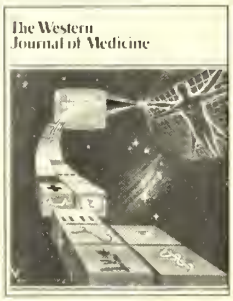

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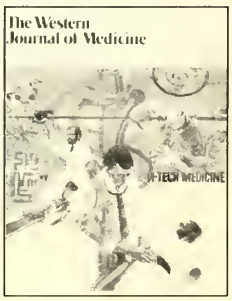

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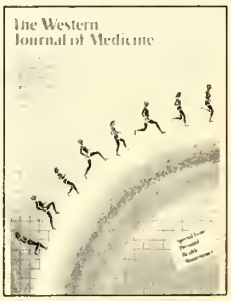

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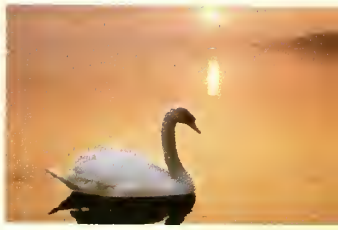

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References: 1. Newton RE, *et al* A review of the side effect profile of buspirone *Am J Med* 1986,80(3B) 17-21 **2.** Lucki I, *et al* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function *Br J Clin Pharmacol* 1987,23 207-211 **3.** Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987,82(5A) 20-26

Contraindications: Hypersensitivity to buspirone hydrochloride

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended BuSpar should not be employed in lieu of appropriate antipsychotic treatment

Precautions: ***General***—*Interference with cognitive and motor performance.* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients. Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures

Possible concerns related to buspirone's binding to dopamine receptors Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia) Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia)

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**) Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers The clinical significance is not clear Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice, buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur

Pregnancy: Teratogenic Effects—Pregnancy Category B Should be used during pregnancy only if clearly needed

Nursing Mothers—Administration to nursing women should be avoided if clinically possible

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement

Associated with Discontinuation of Treatment—The more common events causing discontinuation included central nervous system disturbances (3 4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1 2%), primarily nausea, miscellaneous disturbances (1 1%), primarily headache and fatigue In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials *Cardiovascular* Tachycardia/palpitations 1% *CNS* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2% *EENT* Blurred vision 2% *Gastrointestinal* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal* Musculoskeletal aches/pains 1% *Neurological* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1% *Skin* Skin rash 1% *Miscellaneous* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows Frequent are those occurring in at least 1/100 patients, infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients *Cardiovascular*—frequent nonspecific chest pain, infrequent syncope, hypotension, hypertension, rare cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia *Central Nervous System*—frequent dream disturbances, infrequent depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures, rare feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis *EENT*—frequent tinnitus, sore throat, nasal congestion, infrequent redness and itching of the eyes, altered taste, altered smell, conjunctivitis, rare inner ear abnormality, eye pain, photophobia, pressure on eyes *Endocrine*—rare galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding, rare burning of the tongue *Genitourinary*—infrequent urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria, rare amenorrhea, pelvic inflammatory disease, enuresis, nocturia *Musculoskeletal*—infrequent muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias *Neurological*—infrequent involuntary movements, slowed reaction time, rare muscle weakness *Respiratory*—infrequent hyperventilation, shortness of breath, chest congestion, rare epistaxis *Sexual Function*—infrequent decreased or increased libido, rare delayed ejaculation, impotence *Skin*—infrequent edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters, rare acne, thinning of nails *Clinical Laboratory* infrequent increases in hepatic aminotransferases (SGOT, SGPT), rare eosinophilia, leukopenia, thrombocytopenia *Miscellaneous*—infrequent weight gain, fever, roaring sensation in the head, weight loss, malaise, rare alcohol abuse, bleeding disturbance, loss of voice, hiccoughs

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior)

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress No deaths have been reported in humans either with deliberate or accidental overdosage

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage No specific antidote is known and dialyzability of buspirone has not been determined

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative

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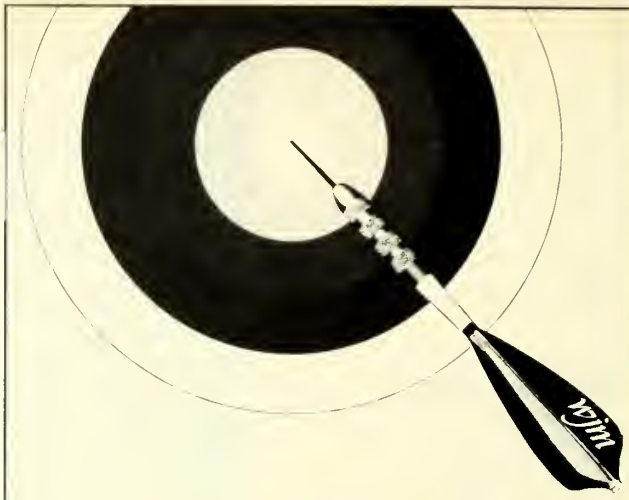

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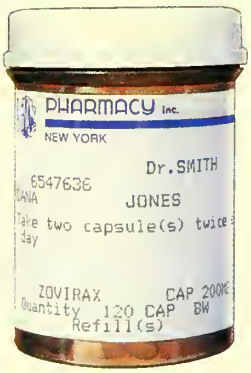

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Genital Herpes Infections: The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs Thus orally administered Zovirax is not appropriate in treating all genital herpes infections The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories.

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes)

Oouble-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing The duration of pain and new lesion formation was decreased in some patient groups The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy Patients with mild disease may derive less benefit than those with more severe episodes In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered Zovirax given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively Serial analyses of the 3 month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time

The frequency and severity of episodes of untreated genital herpes may change over time After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects In general, orally administered Zovirax should not be used for the suppression of recurrent disease in mildly affected patients Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients Oiscussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease Thus, this regimen should be considered only for appropriate patients with annual re-evaluation

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions

Herpes Zoster Infections: In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to Zovirax and 94 to placebo), Zovirax (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to Zovirax and 43 to placebo), Zovirax (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia)

CONTRAINDICATIONS: Zovirax Capsules and Suspension are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations

WARNINGS: Zovirax Capsules and Suspension are intended for oral ingestion only

PRECAUTIONS: **General:** Zovirax has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility) The recommended dosage should not be exceeded (see DOSAGE ANO ADMINISTRATION)

Exposure of Herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients The relationship between the *in vitro* sensitivity of Herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY-Microbiology)

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve Urinary excretion and renal clearance were correspondingly reduced The clinical effects of this combination have not been studied

Carcinogenesis, Mutagenesis, Impairment of Fertility The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes) Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics)

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay

Acyclovir was tested in two *in vitro* cell transformation assays Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters, higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels) In all 4 microbial assays, no evidence of mutagenicity was observed Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in man At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels Results in the other five mammalian cell loci follow at 3 loci in a Chinese hamster ovary cell line the results were inconclusive at concentrations at least 1850 times human levels, at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p o) or in rats (25 mg/kg/day, s c) In the mouse study plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels At a higher dose in the rat (50 mg/kg/day, s c), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels) No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels) In a rat peri- and postnatal study at 50 mg/kg/day s c (11 to 22 times human levels) there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12 5 mg/kg/day and 25 mg/kg/day, s c The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured) However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively caused testicular atrophy Plasma levels were not measured in the one month study and were 24 to 48 times human levels in the six month study Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day, some evidence of recovery of sperm production was evident 30 days postdose Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels No testicular abnormalities were seen in dogs given 50 mg/kg/day i v for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels)

Pregnancy: ***Teratogenic Effects***: Pregnancy Category C Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p o), rabbit (50 mg/kg/day s c and i v) or in standard tests in the rat (50 mg/kg/day s c) These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity In this test, rats were given 3 s c doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels There are no adequate and well-controlled studies in pregnant women Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination

Nursing Mothers. Acyclovir concentrations have been documented in breast milk in two women following oral administration of Zovirax and ranged from 0 6 to 4 1 times corresponding plasma levels These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0 3 mg/kg/day Caution should be exercised when Zovirax is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Herpes Simplex: ***Short-Term Administration***: The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with orally administered Zovirax were nausea and/or vomiting in 8 of 298 patient treatments (2 7%) and headache in 2 of 298 (0 6%) Nausea and/or vomiting occurred in 2 of 287 (0 7%) patients who received placebo

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with orally administered Zovirax (0 3%), included diarrhea, dizziness, anorexia fatigue, edema, skin rash leg pain inguinal adenopathy, medication taste and sore throat

Long-Term Administration The most frequent adverse reactions reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 Zovirax - treated patients were nausea (4 8%), diarrhea (2 4%), headache (1 9%) and rash (1 7%) The 589 control patients receiving intermittent treatment of recurrences with Zovirax for 1 year reported diarrhea (2 7%), nausea (2 4%) headache (2 2%) and rash (1 5%)

The most frequent adverse reactions reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1 5%), rash (1 3%) and paresthesia (0 8%) Reactions reported by 329 patients during the third year include asthenia (1 2%) paresthesia (1 2%) and headache (0 9%)

Herpes Zoster: The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral Zovirax 5 times daily for 7 to 10 days in 323 patients were malaise (11 5%), nausea (8 0%), headache (5 9%), vomiting (2 5%), diarrhea (1 5%) and constipation (0 9%) The 323 placebo recipients reported malaise (11 1%), nausea (11 5%), headache (11 1%), vomiting (2 5%), diarrhea (0 3%) and constipation (2 4%)

OVERDOSAGE: Precipitation of acyclovir in renal tubules may occur when the solubility (2 5 mg/mL) in the intratubular fluid is exceeded Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species rats treated with i v and i p doses of 20 mg/kg/day for 21 and 31 days, respectively and at s c doses of 100 mg/kg/day for 10 days, rabbits at s c and i v doses of 50 mg/kg/day for 13 days, and dogs at i v doses of 100 mg/kg/day for 31 days A 6 hr hemodialysis results in a 60% decrease in plasma acyclovir concentration Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION)

DOSAGE AND ADMINISTRATION **Treatment of initial genital herpes**: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours 5 times daily for 10 days

Chronic suppressive therapy for recurrent disease: 400 mg (two 200 mg capsules or two teaspoonfuls [10 mL] suspension) 2 times daily for up to 12 months, followed by re-evaluation See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily

Intermittent Therapy: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 5 days Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules or four teaspoonfuls [20 mL] suspension) every 4 hours orally 5 times daily for 7 to 10 days

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications

Normal Dosage Regimen (5x daily)	Creatinine Clearance (mL/min/1 73m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval (hrs)
200 mg every 4 hours	> 10	200	every 4 hours 5x daily
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

For patients who require hemodialysis, the dosing schedule should be adjusted so that a dose is administered after each dialysis

References: 1. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection: a multicenter double-blind trial. *JAMA*. 1988;260:201-206. **2.** Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med*. 1988;85(suppl 2A):14-19. **3.** Data on file, Burroughs Wellcome Co., 1990.

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1. Jones JS, Anderson HW Jr, Johnson DW: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

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Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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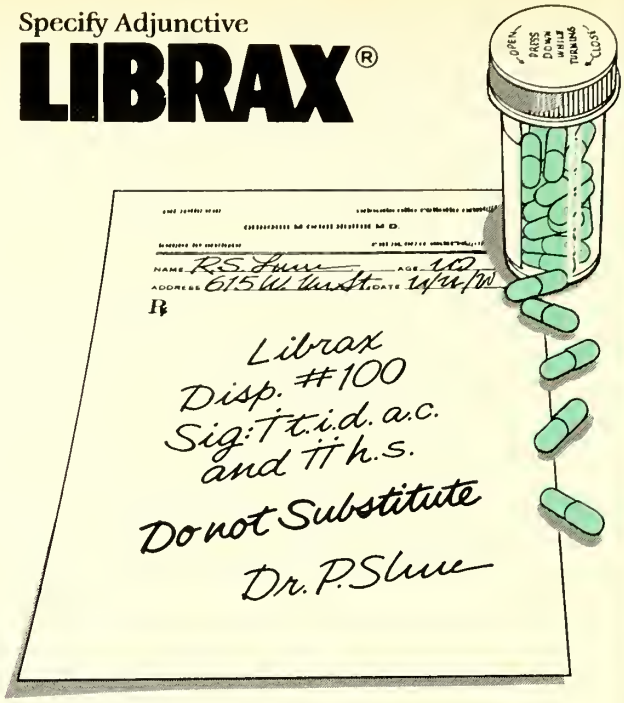

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Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
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Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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ROCHE® Roche Products

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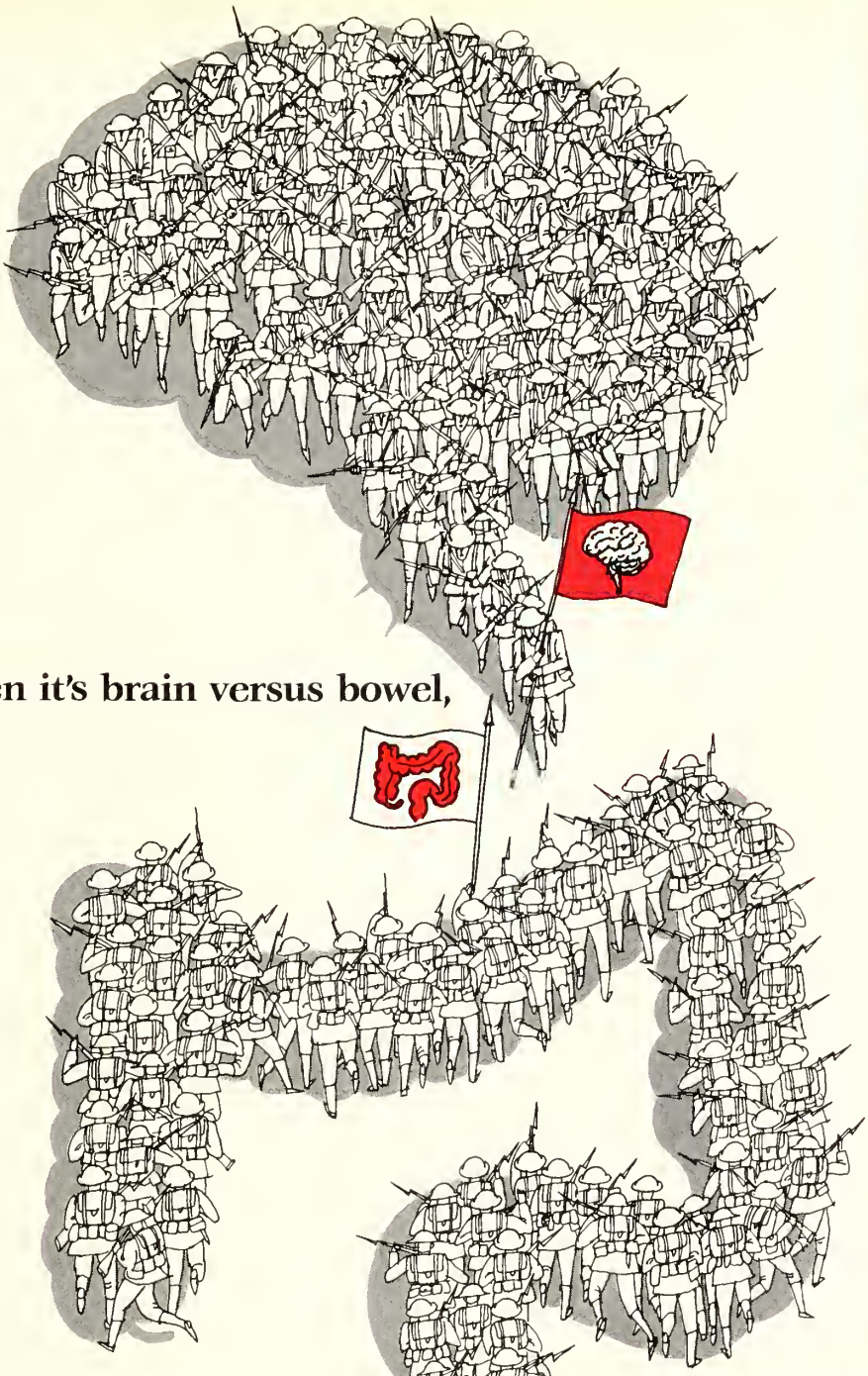

Be sure to specify Librax, "Do not Substitute" or your state's equivalent statement on your prescription.

In IBS,* when it's brain versus bowel,

IT'S TIME FOR THE PEACEMAKER.

In irritable bowel syndrome,* intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict. Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

Specify Adjunctive

LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

ROCHE

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Please see summary of prescribing information on adjacent page.

In Memoriam

California Medical Association

ALWAY, ROBERT H., Stanford. Died Oct 26, 1990, aged 77. Graduate of University of Minnesota, Minneapolis, 1940. Dr Alway was a member of the Santa Clara County Medical Association.

❧

BECKERMAN, STEPHEN B., Fremont. Died Oct 24, 1990, aged 43. Graduate of New York Medical College, 1972. Dr Beckerman was a member of the Alameda-Contra Costa Medical Association.

❧

BERENDSEN, RAYMOND G., Napa. Died Dec 3, 1990, aged 83. Graduate of Loyola University of Chicago, Maywood, Illinois, 1933. Licensed in California in 1933. Dr Berendsen was a member of the Napa County Medical Society.

❧

CALLAGHAN, JOHN H., Redwood City. Died Oct 9, 1990, aged 60. Graduate of Northwestern University Medical School, Chicago, Illinois, 1948. Licensed in California in 1956. Dr Callaghan was a member of the San Mateo County Medical Society.

❧

CLARK, ESTHER B., Palo Alto. Died Oct 4, 1990, aged 90. Graduate of Stanford University, Stanford, California, 1925. Dr Clark was a member of the Santa Clara County Medical Association.

❧

DENNIS, ROBERT L., San Jose. Died Oct 3, 1990, aged 83. Graduate of Stanford University, Stanford, California, 1940. Licensed in California in 1940. Dr Dennis was a member of the Santa Clara County Medical Association.

❧

FARELLY, LAURENCE, Visalia. Died Sep 4, 1990, aged 72. Graduate of University of Manitoba, Canada, 1953. Dr Farelly was a member of the Tulare County Medical Society.

❧

HOPP, EUGENE S., San Francisco. Died Oct 19, 1990, aged 80. Graduate of Medical College of Georgia, Augusta, 1937. Dr Hopp was a member of the San Francisco Medical Society.

HYSLOP, CHARLES P., San Diego. Died Oct 9, 1990, aged 66. Graduate of Columbia University, New York, New York, 1947. Dr Hyslop was a member of the San Diego County Medical Society.

❧

JOHNSON, VICTOR P., Riverside. Died Nov 1990, aged 73. Graduate of University of Colorado, Denver, 1951. Licensed in California in 1961. Dr Johnson was a member of the Riverside County Medical Association.

❧

KRICK, JAMES A., Walnut Creek. Died Oct 10, 1990, aged 50. Graduate of Cornell University, New York, New York, 1967. Dr Krick was a member of the Alameda-Contra Costa Medical Association.

❧

LAMOTTE, JOHN L., San Mateo. Died Nov 17, 1990, aged 82. Graduate of University of Southern California, Los Angeles, 1940. Dr Lamotte was a member of the San Mateo County Medical Society.

❧

LARMORE, RICHARD WRIGHT, Rancho Mirage. Died Oct 1, 1990, aged 42. Graduate of Indiana University School of Medicine, Indianapolis, 1974. Dr Larmore was a member of the Riverside County Medical Association.

❧

LEAVITT, ARTHUR S., Los Angeles. Died Oct 17, 1990, aged 93. Graduate of University of Manitoba Faculty of Medicine, Winnipeg, 1924. Licensed in California in 1924. Dr Leavitt was a member of the Los Angeles County Medical Association.

❧

LEWIS, CHARLES F., Jr, Oakland. Died Nov 30, 1990, aged 75. Graduate of University of Louisville School of Medicine, Kentucky, 1940. Licensed in California in 1940. Dr Lewis was a member of the Alameda-Contra Costa Medical Association.

❧

LOEHR, ROBERT A., San Jose. Died Dec 5, 1990, aged 75. Graduate of Stanford University, Stanford, California, 1941. Dr Loehr was a member of the Santa Clara County Medical Association.

LOGAN, LLOYD H., San Francisco. Died Aug 11, 1990, aged 73. Graduate of Northwestern University Medical School, Chicago, Illinois, 1946. Licensed in California in 1946. Dr Logan was a member of the San Francisco Medical Society.

❧

LUKE, MAURICE R., San Mateo. Died Nov 11, 1990, aged 69. Graduate of Stanford University, Stanford, California, 1946. Dr Luke was a member of the San Mateo County Medical Society.

❧

PRINCE, PAUL W., Los Angeles. Died Oct 25, 1990, aged 82. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1931. Licensed in California in 1931. Dr Prince was a member of the Los Angeles County Medical Association.

❧

SPIERER, EUGENE, Los Angeles. Died Sep 12, 1990, aged 81. Graduate of University of Illinois College of Medicine, Chicago, 1946. Licensed in California in 1947. Dr Spierer was a member of the Los Angeles County Medical Association.

❧

WOLFF, MARVIN L., Berkeley. Died Dec 6, 1990, aged 66. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1947. Dr Wolff was a member of the Alameda-Contra Costa Medical Association.

Denver Medical Society

SUTTON, PAUL. Died Nov 28, 1990, aged 82. Graduate of Loyola University of Chicago Strich School of Medicine, 1939. Licensed in Colorado in 1956.

❧

WEIKER, JUSTIN. Died Oct 1990, aged 81. Licensed in Colorado in 1935.

Idaho Medical Association

BARCLAY, ALEXANDER, Coeur d'Alene. Died Oct 1990, aged 78. Graduate of Vanderbilt University, Nashville, Tennessee, 1937. Licensed in Idaho in 1938. Dr Barclay was a member of the Koatenai-Benewah County Medical Society.

Utah Medical Association

BARTHOLOMEW, HENRY H., Salt Lake City. Died Oct 4, 1990, aged 69. Graduate of University of Pennsylvania, Philadelphia, 1950. Licensed in Utah in 1956. Dr Bartholomew was a member of the Salt Lake County Medical Society.

The most prescribed calcium channel blocker for hypertension[1] gets even better

INTRODUCING ONCE-A-DAY VERELAN®

Verapamil HCl 120 mg 240 mg

PELLET-FILLED CAPSULES

Verapamil without the food variable

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Predictable controlled absorption over 24 hours with or without food

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Administration with or without food removes a significant barrier to convenient treatment

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Once-daily dosage regardless of dose

Constipation, which can be easily managed in most patients, is the most frequently reported side effect of verapamil.

Reference:

1. Adapted from Pharmaceutical Data Services, Alpha Data Services, December 1989.

Brief Summary
VERELAN® Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY: Food does not affect the extent or rate of the controlled absorption of verapamil from the VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS: Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- and third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility, there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk, therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS: In clinical trials with 285 hypertensive patients on VERELAN *verapamil HCl* for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%), myalgia (1.1%). In clinical trials at other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 10%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%), edema (1.9%); headache (2.2%), rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%), bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain.

Cardiovascular: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

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Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

February 14-16—**Emergency Medicine Update.** U of A, Tucson. Thurs-Sat. Contact: Carroll Morrow, (602) 626-6312.

February 14-17—**State-of-the-Art Echocardiography: Color Flow Imaging, Transecophageal Echocardiography, Diastolic Function, Intravascular and Digital Echo.** American College of Cardiology at Tucson. Thurs-Sun. Contact: Extramural Programs, ACC, (800) 253-4636.

February 15-17—**Anesthesia for the '90s: 17th Annual Scientific Meeting.** Arizona Society of Anesthesiologists at Wyndham Paradise Valley Resort, Paradise Valley. Fri-Sun. Contact: Beverly Reichter, (602) 246-8901.

February 21-23—**17th Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell, (602) 820-7027.

February 24-27—**Fourth International Workshop in Chromosomes and Solid Tumors.** U of A at Doubletree Inn, Tucson. Mon-Thurs. Contact: Jeffrey Trent, PhD, (602) 626-6408.

February 25-28—**Practical Radiology.** U of A at Loews Ventana Canyon Resort, Tucson. Mon-Thurs. Contact: Anita Russell, (602) 626-7832.

February 28-March 2—**Complications in Vascular Surgery.** U of A at Loews Ventana Canyon, Tucson. Thurs-Sat. Contact: Anita Russell, (602) 625-7832.

February 28-March 2—**13th Annual Postgraduate Course: Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix OB/GYN Society at the Scottsdale Hilton Hotel, Scottsdale. Thurs-Sat. Contact: (602) 266-6321.

February 28-March 3—**Arizona Academy of Family Physicians Annual Scientific Assembly.** Scottsdale Plaza Resort. Thurs-Sun. Contact: Nancy Reeves, (602) 249-2021.

March 1-2—**Geriatric/Nutrition Conference.** Rural Health Office, U of A, Tucson, Fri-Sat. Contact: Christy Snow, (602) 626-7946.

March 2—**ENT for the Primary Care Physician.** Ashton B. Taylor Auditorium, Mayo Clinic-Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

March 3-6—**Fiberoptics Workshops for the Difficult Airway.** University of Michigan Medical School, Department of Anesthesiology, at the Red Lion's Posada Resort, Scottsdale. Sun-Wed. Contact: Julie Jacobs, (800) 962-3555.

March 14-16—**The Modern Surgical Management of Endometriosis.** U of A at Registry Resort, Scottsdale. Thurs-Sat. Contact: Shirley Rodriguez, (602) 265-1112.

March 15-16—**Ophthalmology Spring Symposium.** U of A, Tucson. Mon-Tues. Contact: Anita Russell, (602) 626-7832.

March 16-20—**Fifth Annual Magnetic Resonance Imaging Conference.** Barrow Neurological Institute at Marriott's Camelback Inn, Scottsdale. Sat-Wed. Contact: Kevin King, RT, (602) 285-3956.

March 24-27—**Management Strategies in Complex Congenital Heart Disease.** Mayo Clinic, Rochester, Minn, at Marriott's Camelback Inn, Scottsdale. Sun-Wed. Contact: Bonita Walin, (800) 323-2688.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901

Mayo Clinic-Scottsdale—Contact. Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact. University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

April 9-12—**Primary Care Update.** U of A, Tucson. Tues-Fri. Contact: Debbie Stymore, (602) 626-7736.

April 25—**Clinical Reviews 1991.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Thurs. Contact: Mayo Clinic-Scottsdale.

April 27—**Gastroenterology: Update for the Family Practitioner.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Sat. Contact: Mayo-Clinic Scottsdale.

April 27—**Urology for the Primary Care Physician.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

March 23-24—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Newport Beach Marriott. Sat-Sun. 9 hrs. $150. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 16-19—**California Society of Anesthesiologists Annual Meeting.** CSA at Marriott Hotel, Anaheim. Thurs-Sun. 20 hrs. $175. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

CARDIOLOGY

March 22-23—**Coronary Heart Disease Update.** Medical Education Resources at Hyatt Regency Alicante, Anaheim. Fri-Sat. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

April 2-4—**1st Annual Symposium of Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. $750. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 19-20—**Cardiac Diagnostic Methods and Risk Management.** Medical Education Resources at San Diego Hilton. Fri-Sat. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

April 22-May 1—**Cardiology for the Consultant: A Physician's Retreat.** Scripps Clinic and Research Foundation at Inn Rancho Santa Fe. 1½ wks. Contact: Mary Ann Morris, 860 SW Scherer Rd, Lee's Summit, MO 64063. (816) 524-5780.

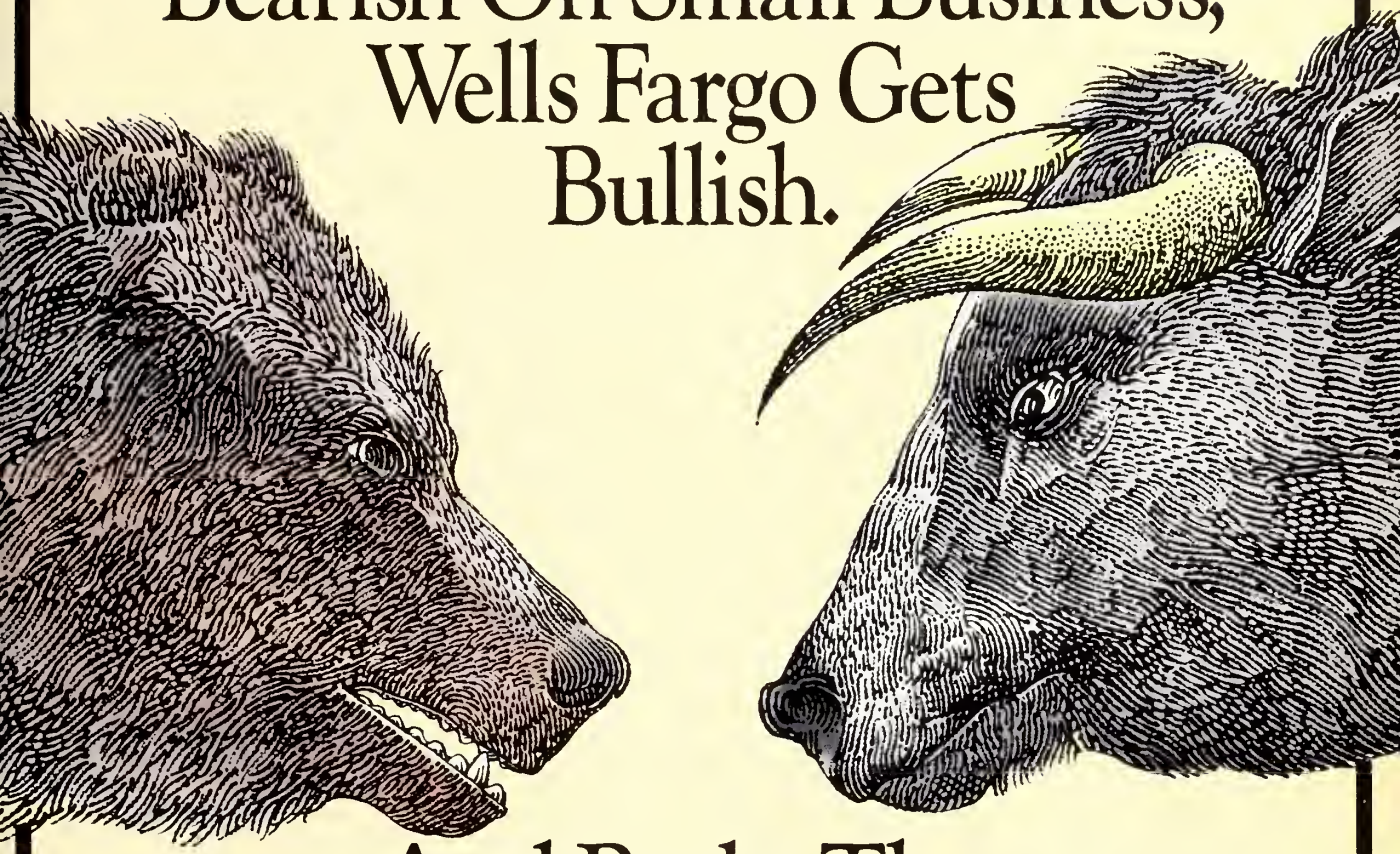
June 21-22—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

July 19-21—**Contact Dermatitis: The Basics.** Stanford at Hotel Meridien, San Francisco. Fri-Sun. Contact: Pamela Bain, Dept of Dermatology, Room R-122, Stanford 94305. (415) 723-7854.

(Continued on Page 154)

While Other Banks Get Bearish On Small Business, Wells Fargo Gets Bullish.



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(Continued from Page 152)

EMERGENCY MEDICINE

February 24-March 1—**Annual Emergency Medicine.** UCD at Hyatt Lake Tahoe, Incline Village, NV. Sun-Fri. 25 hrs. $465. Contact: UCD.

March 10-15—**12th Annual Mammoth Mountain Emergency Medicine Ski Conference.** CAL/ACEP at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Medical Conferences, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 18-22—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

April 3-6—**Advances in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Sat. 22 hrs. $435. Contact: UCSF.

April 13—**Critical Care Medicine.** Grossmont Hospital at San Diego Convention Center. Sat. 6 hrs. Contact: Verda Belyeu, Grossmont Hospital, Box 158, La Mesa 92044-0158. (619) 589-4153.

May 6-10—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. 32 hrs. $485. Contact: UCSD.

June 8-9—**Clinical Toxicology and Emergency Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $310. Contact: UCSF.

June 24-28—**Postgraduate Institute for Primary Care & Emergency Physicians Emergency Medicine Symposium III: Pediatrics, OB/GYN, Dermatology, Legal Aspects, Etc.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $260-$485. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

February 15-17—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 15-18—**43rd Scientific Assembly of the California Academy of Family Physicians.** CAFP at Wyndham Hotel, Palm Springs. Fri-Mon. 23 hrs. Contact: Robert Fagan, (415) 541-0762.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Research Foundation and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

March 15-17—**Psychopharmacology for the Primary Care Physician.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 16—**Orthopedics and Sports Medicine in Primary Care.** Scripps Clinic and Research Foundation at Amphitheater of the Green Hospital, La Jolla. Sat. 6 hrs. $125. Contact: Laurie Jones, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

March 22-23—**Management of Occupational Health Problems in Primary Care Settings.** UC Berkeley at Le Baron Hotel, San Jose. Fri-Sat. $225. Contact: Marion Gillen, (415) 642-5507.

March 27-29—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Cathedral Hill Hotel, San Francisco. Wed-Fri. 16 hrs. Contact: UCSF.

April 6-13—**Primary Care Medicine: Update '91.** UCSF at Waiohai Kauai, Hawaii. 1 week. 20 hrs. $525. Contact: UCSF.

April 26-28—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village, San Diego. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 10-14—**UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

July 8-11—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

INTERNAL MEDICINE

February 15-17—**24th Annual Recent Advances in Neurology.** UCSF at San Francisco. Fri-Sun. 15 hrs. Contact: UCSF.

February 18-20—**Clinical Hematology and Oncology: 1991.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 1—**17th Annual Diabetes Symposium.** UCD at Sheraton Hotel, Sacramento. Fri. 6 hrs. $140. Contact: UCD.

March 6-7—**Advances in Endocrinology and Metabolism.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 8-9—**Diabetes Update.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

March 9—**Breast Cancer Controversies in the 1990s.** Good Samaritan Hospital Cancer Institute at San Jose. Sat. 6 hrs. Contact: Cindy Taormino, (408) 559-2458.

March 11-15—**29th Annual Symposium on Critical Care Medicine.** Mon-Fri. 25 hrs. $435-$670. Contact: USC.

March 15-21—**Internal Medicine 1991: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 23—**Diabetes Care Program, "New Pathways for the '90s."** Grossmont Hospital at San Diego Princess Hotel. Sat. 6 hrs. $100. Contact: Terri Francis, (619) 589-4810.

April 20—**Growth Factors in Clinical Medicine.** Scripps Clinic and Research Foundation at La Jolla. Sat. 4 hrs. $75. Contact: Laurie Jones, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

May 13-17—**Advances in Internal Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $585. Contact: UCSF.

May 25-27—**1991 CSIM Annual Meeting: Controversies, Challenges, Changes, and Calamari.** CSIM at Monterey Plaza Hotel. Sat-Mon. Contact: Cynthia Eaton, CSIM, Box 880606, San Francisco 94188-0606. (415) 882-5198.

OB/GYN

February 14-17—**46th Annual Postgraduate Assembly.** OB-GYN Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB-GYN Assembly, 5820 Wilshire Blvd, No. 500, Los Angeles 90036. (213) 937-5514.

March 9—**Infertility Update VI.** Scripps Clinic and Research Foundation. Sat. 7 hrs. $145. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

KEY TO ABBREVIATIONS

CMA California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 156)

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*21-day parallel group comparative study in patients with psoriasis measuring improvement in total disease signs score from baseline at 21 days; 60% with ELOCON (n=98); 37% with triamcinolone (n=97); (p<0.01). Interim measurement of improvement reported at 4 days; 28% with ELOCON; 18% with triamcinolone

†The difference in burning and itching was lower with ELOCON than with triamcinolone ointment (ELOCON 1% and 2% respectively, triamcinolone 3% and 6% respectively)

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BRIEF SUMMARY

Cream 0.1%
Ointment 0.1%
Lotion 0.1%
For Dermatologic Use – Not for Ophthalmic Use

INDICATIONS AND USAGE ELOCON **Cream, Ointment,** and **Lotion,** are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

CONTRAINDICATIONS ELOCON **Cream, Ointment,** and **Lotion,** are contraindicated in patients who are hypersensitive to mometasone furoate, to other corticosteroids, or to any ingredient in these preparations

PRECAUTIONS **General:** Systemic absorption of potent topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients

Conditions which augment systemic absorption include application of more potent steroids, application of steroids in optimized vehicles, use over large surface areas, prolonged use, use in areas where the epidermal barrier is disrupted, and the use of occlusive dressings. (See **DOSAGE AND ADMINISTRATION.**)

Patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See **PRECAUTIONS – Pediatric Use.**)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted

In the presence of dermatological infections, use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled

Laboratory Tests The following tests may be helpful in evaluating HPA axis suppression
Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids

Genetic toxicity studies with mometasone furoate, which included the Ames test, mouse lymphoma assay, and a micronucleus test, did not reveal any mutagenic potential

Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies of teratogenic effects from topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use: *Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio*

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children

ADVERSE REACTIONS The following local adverse reactions were reported with ELOCON **Cream** during clinical studies with 319 patients: burning, 1, pruritus, 1, and signs of skin atrophy, 3

The following local adverse reactions were reported with ELOCON **Ointment** during clinical studies with 812 patients: burning, 13, pruritus, 8, skin atrophy, 8, tingling/stinging, 7, and furunculosis, 3

The following local adverse reactions were reported with ELOCON **Lotion** during clinical studies with 209 patients: acneiform reaction, 2, burning, 4, and itching, 1. In an irritation/sensitization study with 156 normal subjects, folliculitis was reported in 4

The following local adverse reactions have been reported infrequently when other topical dermatologic corticosteroids have been used as recommended. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria

OVERDOSAGE Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS.**)

DOSAGE AND ADMINISTRATION Apply a thin film of ELOCON **Cream** or **Ointment** to the affected skin areas once daily. Do not use occlusive dressings

Apply a few drops of ELOCON **Lotion** to the affected areas once daily and massage lightly until it disappears. For the most effective and economical use, hold the nozzle of the bottle very close to the affected areas and gently squeeze

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CONTINUING MEDICAL EDUCATION

(Continued from Page 154)

March 13-17—**Gynecologic Surgery with Special Emphasis on Pre-Invasive Neoplasia and Urogynecology.** UCI/Memorial Center for Health Education at La Quinta Hotel Golf & Tennis Resort, Palm Springs. Wed-Sun. Contact: UCI.

April 10-14—**Pacific Coast Fertility Society Annual Scientific Program.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No 500, Los Angeles 90036. (213) 937-5514.

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

March 13-17—**Mountain Medicine: '91.** American College of Emergency Physicians at Squaw Valley. Wed-Sun. 22 hrs. $395. Contact: Howard Donner, MD, PO Box 321, Yreka 96097. (800) 888-5632.

OPHTHALMOLOGY

March 23—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. $120. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

May 17-19—**California Association of Ophthalmology Annual Meeting.** CAO at Sheraton Grande Torrey Pines, La Jolla. Fri-Sun. Contact: Linda Xyz, (415) 777-3937.

PATHOLOGY

April 6—**6th Annual Conference: New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Amphitheater of Green Hospital, La Jolla. Sat. 7 hrs. $125. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

April 17-19—**12th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. $395. Contact: UCSF.

July 15-19—**Advances in Gastroenterology.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 19-22 hrs. $425. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

PEDIATRICS

February 18-20—**Pediatrics Update: 1991.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5-6—**Annual Ambulatory Pediatrics.** UCD at Radisson Hotel, Sacramento. Fri-Sat. Contact: UCD.

April 11-13—**Nevada Neonatal-Pediatric Conference.** Humana Children's Hospital at Sands Hotel and Casino, Las Vegas. Thurs-Sat. 15 hrs. $200. Contact: Evelyn Bethel, (702) 733-4944.

April 13-14—**Pediatric Update 1991.** Children's Hospital Oakland at Jack London's Waterfront, Oakland. Sat-Sun. 11 hrs. $250. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

April 18-19—**10th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. Contact: UCD.

May 16-18—**24th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 1—**Special Children: Pediatric Perspectives in the '90s.** Children's Hospital at Merritt Peralta Health Education Center, Oakland. Sat. 7 hrs. $150. Contact: Kim Leadon, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

June 21-23—**Current Concepts in Child Neurology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 15 hrs. Contact: Children's Hospital, (619) 576-4072.

PSYCHIATRY

February 23-24—**The Male Mystique: New Perspectives on the Psychology of Men.** San Diego Psychoanalytic Society and Institute at Hotel del Coronado, San Diego. Sat-Sun. Contact: Joyce Harding, SDPSI, 1010 Turquoise St, Ste 320, San Diego 92109-1259. (619) 488-0687.

February 28-March 1—**The Dimensions of Caring 1991: A Symposium on Palliative Care of the Cancer Patient.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Fri. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

(Continued on Page 165)

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ANNUAL SESSION

MARCH 8 THROUGH 13

WESTERN SCIENTIFIC ASSEMBLY

RENO-SPARKS CONVENTION CENTER
AND BALLY'S HOTEL/RENO, NEVADA

YOU ARE INVITED

GOLDEN APPLE AWARD RECEPTION

Ruminations of a Teaching Surgeon

Friday, March 8, 5:30 pm

Bally's Hotel

Robert A. Chase, MD, Emile Holman Professor of Surgery and Professor of Anatomy at Stanford University, has been selected by the Committee on Scientific Assemblies to receive CMA's 1991 Golden Apple Award. This award spotlights exceptional physicians who have made a lifelong commitment to teaching and are renowned for their charismatic, scientific and educational talents. Doctor Chase came to Stanford's Department of Surgery in 1963 from Yale University, his alma mater. He has received teaching awards at both Yale and Stanford, served as a visiting professor at numerous institutions, and is a member of a large number of national, professional associations. Doctor Chase serves on a variety of editorial boards and has published in excess of a hundred professional papers and authored two books on surgery of the hand.

The award will be presented during a reception, where Doctor Chase will honor us with a short presentation, "Ruminations of a Teaching Surgeon." All are invited to attend. Come help us honor this outstanding teacher who has touched the lives of many California physicians.

The financial assistance of Cooperative of American Physicians, Inc.-Mutual Protection Trust is gratefully acknowledged in making this reception possible.

California Medical Association's 1991 Annual Session and Western Scientific Assembly will be held March 8 - 10 at Bally's Hotel and the Reno/Sparks Convention Center in Reno, Nevada.

For more information on the following programs, please contact Anna Durante at CMA (415) 882-5184

Friday, March 8

01 Basic Cardiac Life Support

02 Basic Colposcopy for the Primary Care Physician

03 Preventing Occupational Lead Toxicity

04 The Basics in Pain Management

05 The Changing Face of Infectious Disease

06 Practical Therapies in Pulmonary Diseases

07 What Doctors Should Know About Aids: An Up-To-The-Minute Update

08 Cumulative Trauma Disorders - The Epidemic of the 1990s

09 "I See" Eye Care for the Primary Care Physician

10 Cracked Forever? Developmental Disabilities in Infants Born to Addicted Mothers

Saturday, March 9

11 "Must Your Patient Suffer?" Acute, Chronic, and Cancer Pain

12 Advanced Cardiac Life Support: Certification Course

13 Things Happen...Topics in Emergency Medicine

14 Prevention on the Front Lines

YOU ARE INVITED

15 Practice Guidelines: Standards of Quality Care, Cookbook Medicine, or Invitation to Law Suits?

16 The Top of the Shoulder: The State of the Art in Diagnosis and Treatment

17 How Do I Treat Common Ear Problems?

18 What's New in the Diagnosis and Treatment of Rhinitis and Sinusitis

19 Primary Care Dermatology - Hot Topics

20 Managing Diabetes in the 1990s

21 Seizure Update

22 The Challenges of Treating Adolescent Patients

23 Planning for Retirement and a Stable Financial Future

Sunday, March 10

24 Advanced Cardiac Life Support: Recertification Course

25 Prevention of Head and Spinal Cord Injuries

26 Diagnosis and Treatment of Hand Injuries

27 Chronic Fatigue Syndrome and Premenstrual Syndrome: Controversial Issues

28 Imaging in the 90s: Update for the Primary Care Physician

29 Urology for Family Practitioners 1991

30 Maintaining Excellence in Ambulatory Care

31 When Smoke Gets in Your Eyes - How to Enact Tobacco Control Ordinances in Your Community

32 Program Cancelled

33 Skin Cancer - How Can I Prevent It? How is it Treated?

34 CMA Takes a Critical Look At the Washington Scene

35 Physicians and the Law

DISTINGUISHED SPEAKER

Sunday, March 10, 1991

1:00 pm

Reno/Sparks Convention Center

Renoir: His Art and Arthritis

Doctor James S. Louie, Professor of Medicine and Chief of the Division of Rheumatology at Harbor/UCLA Medical Center, will offer a unique presentation on the life of Pierre Auguste Renoir, illustrated with slides of the famed artist's life and work that captures the artist's determination, family support and medical care that enabled him to continue his career in spite of severely crippling disease.

Doctor Louie credits his wife with the origin of his interest in Renoir's art and arthritis. A docent at Los Angeles County Museum of Art, she remarked about the painter's arthritic condition, enkindling her husband's professional curiosity. Over the past 10 years, Doctor Louie's growing interest has taken him into the libraries and back rooms of museums from Paris to Chicago, including a meeting with Renoir's son, Jean, who greatly enriched his knowledge and understanding. Through his research, Doctor Louie has gained insight into Renior the man, the artist, and the arthritic. Come and enjoy this fascinating and inspirational walk through Renoir's life as few have viewed it. All are invited to attend.

YOU ARE INVITED

CONCURRENT EVENTS

CMA HOUSE OF DELEGATES

The CMA House of Delegates meets each day, Saturday, March 9 through Wednesday, March 13 at Bally's Hotel. Sit in on reference committee hearings and House sessions to see firsthand how CMA policies are shaped. Highlights of this year's House will be the farewell address of CMA President, Charles W. Plows, MD, an Anaheim obstetrician-gynecologist, and the inaugural address of CMA's President-Elect, Howard L. Lang, MD, a Greenbrae obstetrician-gynecologist. Registration will be available March 8 - 13 at Bally's Hotel.

YOUNG PHYSICIANS SECTION ANNUAL ASSEMBLY

The CMA established the Young Physicians Section (YPS) in March 1989 to represent physicians who are CMA members under the age 40 or in the first five years of practice. During the Assembly, representatives will elect officers for the Section and discuss issues of interest and concern to young physicians. The Assembly will also feature presentations from Eugene Ogrod, MD, Vice-Chair of the CMA Council, and H. Rex Greene, MD, a CMA Council member from Los Angeles. Doctors Ogrod and Greene will speak to the Assembly concerning effective leadership in organized medicine. Registration will begin at 12:30 pm on Friday, March 8 at Bally's Hotel, and the Assembly will convene from 1:30 to 5:00 pm in room Capitol #1.

SPECIAL EVENTS 1991

In cooperation with Safaris, Inc., CMA will offer convention registrants and their families a variety of fun-filled events in the Reno, Nevada area. Registrations can be made at the SAFARIS OFFICE located at the South entrance of Bally's Hotel lobby.

- **Reno City Gaming Tour**
- **Virginia City Tour**
- **Lake Tahoe Cruise**
- **Progressive Cooks Tour**

In addition, CMA will offer both Pre- and Post-Convention Ski Packages through the Resort at Squaw Creek. For further information, call 1-800-3CREEK3 and identify yourself with the California Medical Association.

GENERAL INFORMATION

LOCATION

The CMA 1991 Western Scientific Assembly will be held at the Reno/Sparks Convention Center, 2500 East Second Street, Reno, NV 89595. Bally's will be CMA's Convention Headquarters. For hotel reservations call (702) 789-2000.

REGISTRATION FEES

There is no general registration fee for CMA members, Auxiliary members, fellows, residents, interns and medical students, nor to their guests who do not attend educational programs.

Nonmember physicians are required to pay a general registration fee of $120 per day or $300 for the entire event; nurses and allied health professionals are required to pay a $50 fee.

ADVANCE REGISTRATION CLOSES FEBRUARY 15, 1991.

Attendees may register on site at the General Registration Desk located in the Concourse of the Reno/Sparks Convention Center from Thursday, March 7 through Sunday, March 10.

Preregistered members of the House of Delegates, CMA-HMSS representatives, CMA-Auxiliary, and Component and Medical Specialty Societies must pick up their packets at the Registration Desk located in the Grand Salon of Bally's Hotel from Thursday, March 7 through Saturday, March 9.

ANY QUESTIONS?

Contact CMA, Western Scientific Assembly
(415) 882-5184

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(Continued from Page 156)

March 2-3—**Basic Hypnosis: A Hands-On Workshop.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 16 hrs. $195-$295. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034. (213) 475-1260.

March 2-3, March 16-17—**Basic Workshop in Clinical Hypnosis.** San Francisco Academy of Hypnosis at Letterman Army Medical Center. 2 weekends. 24 hrs. $350. Contact: Jan Brooks, (415) 826-0533.

April 27-28—**The Cutting Edge: Being a Better Therapist.** UCSD at La Jolla Marriott, San Diego. Sat-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

RADIOLOGY

March 1-3—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 4-8—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 16-18—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. 16 hrs. $350. Contact: UCSF.

April 7-12—**Diagnostic Imaging: 1991.** UCSF at Ritz-Carlton Mauna Lani, Kona, Hawaii. Sun-Fri. 23 hrs. $595. Contact: UCSF.

April 21-26—**11th Annual San Diego Resident's Radiology Review Course.** UCSD at Hyatt Regency Hotel, La Jolla. Sun-Fri. 39 hrs. $435. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 27—**Introduction to Interventional Radiology.** UCSD at Hyatt Regency Hotel, La Jolla. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 18-21—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, Coronado. Thurs-Sun. 19.5 hrs. $400. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-24—**Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Wed. 14 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 25-28—**5th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 18 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

February 18-20—**11th Betty Ford Center Conference on Chemical Dependency.** Annenberg Center for Health Science. Mon-Wed. Contact: ACHSE, 39000 Bob Hope Dr, Rancho Mirage 92270. (800) 321-3690.

March 6-8—**11th Annual Current Approaches to Radiation, Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $325. Contact: UCSF.

May 17-18—**What's New in Rehabilitation?** Memorial/UCI Center for Health Education at Queen Mary, Long Beach. Fri-Sat. Contact: UCI.

SURGERY

March 21-23—**Annual Aesthetic Surgery Symposium: Aesthetic Surgery of the Breast.** UCSF and Davies Medical Center. Thurs-Sat. Contact: UCSF.

April 29-May 1—**11th Annual Scientific Meeting and Exhibition.** American Society for Laser Medicine and Surgery at the Sheraton on Harbor Island, San Diego. Mon-Wed. Contact: ASLMS, 2404 Stewart Square, Wassau, WI 54401. (715) 845-9283

May 2-4—**Advances in Knee Reconstruction Surgery: Ligament Reconstruction, Unicompartmental Replacement, and Patellofemoral Joint.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 26-hrs. $600. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 15-19—**13th Annual Wound Management Workshop: May.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: UCSD.

MULTIPLE TOPICS

February 21-24—**5th National Forum on AIDS and Chemical Dependency.** American Society of Addiction Medicine at Stanford Court Hotel, San Francisco. Thurs-Sun. 12-16 hrs. Contact: Meeting and Travel Services, Inc, Box 81691, Atlanta, GA 30366. (404) 458-3382.

March 7-9—**Recent Advances in Geriatric Medicine: New Treatment Options for Old Problems.** UCSD at Pan Pacific Hotel, San Diego. Thurs-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 22-23—**Women's Nutrition and Health: Annual Clinical Nutrition Program.** UCD at Embassy Suites, Napa. Fri-Sat. 13 hrs. Contact: UCD.

April 19-20—**HIV Update.** UCD at Holiday Inn Holidome, Sacramento. Fri-Sat. 12 hrs. Contact: UCD.

April 25-28—**Nevada State Medical Association Annual Meeting.** NSMA at Quail Lodge, Carmel. Thurs-Sun. Contact: Nevada State Medical Association, 3660 Baker Ln, Reno, NV 89502. (702) 825-6788.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

February 16-23—**17th Annual Obstetrics and Gynecology Conference.** Rose Medical Center, Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 16-23—**16th Annual Internal Medicine Conference.** Rose Medical Center at Lion Square Lodge, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 23-March 2—**16th Annual General Surgery Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

February 23-March 2—**Fourth Annual Medical Care in the '90s Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 2-9—**13th Annual Pediatrics Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 2-9—**Second Annual Infectious Disease Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 9-16—**16th Annual Primary Care Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 9-16—**Second Annual "Minding the Body, Mending the Mind: Influencing Health and Healing" Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**14th Annual Urology Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**13th Annual Sports Medicine Conference.** Rose Medical Center, Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**Computers in Medicine Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 23-30—**14th Annual Cancer Treatment Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

(Continued on Page 167)

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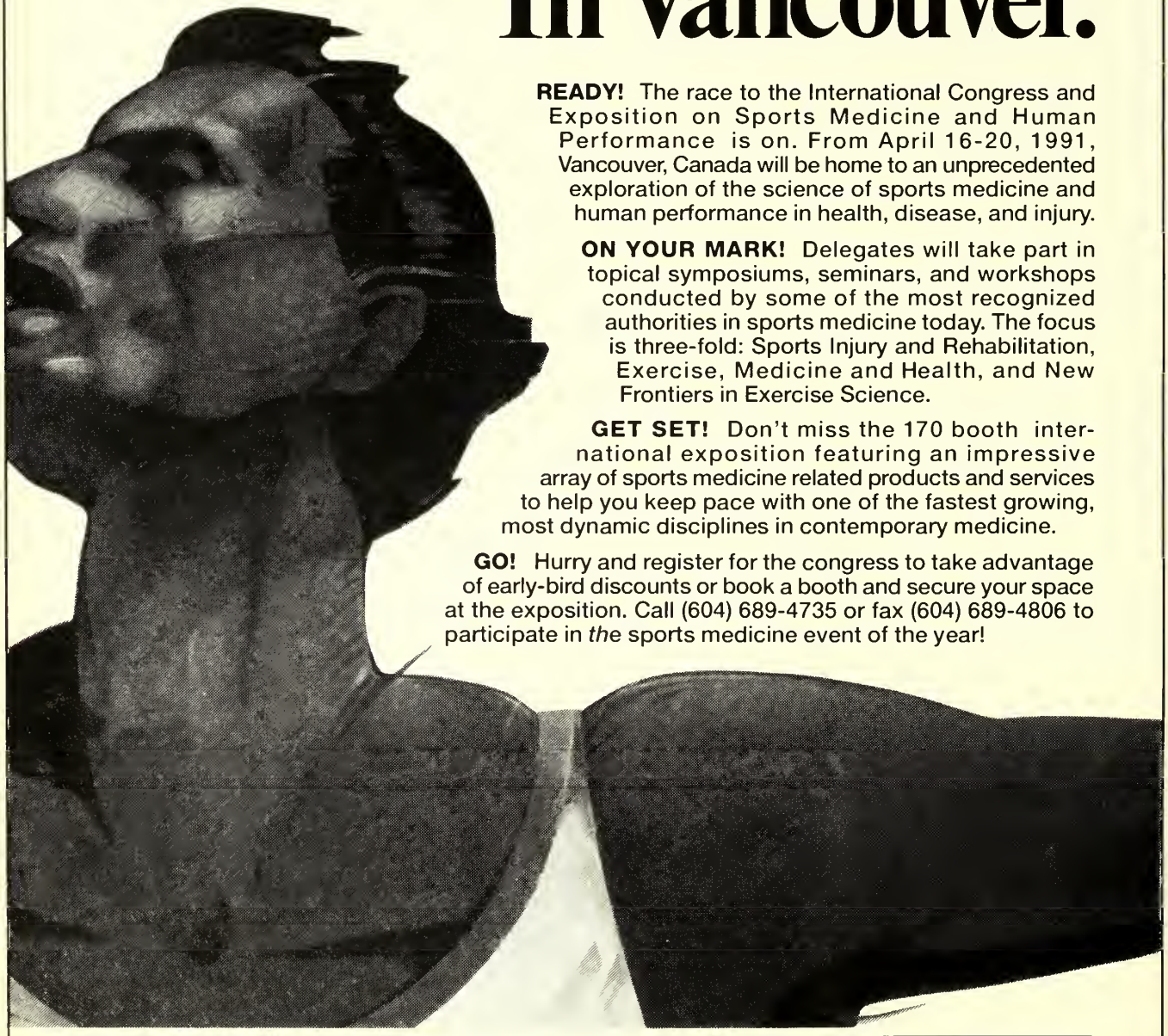

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CONTINUING MEDICAL EDUCATION

(Continued from Page 165)

IDAHO

February 27-March 2—**Sun Valley Program.** Pierce County Medical Society (Washington) College of Medical Education at Sun Valley. Wed-Sat. Contact: PCMS CME, 705 S 9th, No. 203, Tacoma, WA 98405. (206) 627-7137.

March 1-3—**Ada County Medical Society 32nd Annual Medical Winter Clinics—Yuppie Diseases—Ills and Ailments of a Generation.** Shore Lodge, McCall. Fri-Sun. 9 hrs. $100. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 21-22—**Idaho Thoracic Society—Annual Medical Symposium.** Anderson Center, Boise. Thurs-Fri. Contact: Idaho Thoracic Society, PO Box 33, Boise 83707. (208) 344-6567.

April 25-28—**Comprehensive Review in Toxicology.** Idaho Poison Center, Boise. Thurs-Sun. 20 hrs. Contact: Dennis Emerson or Robin Clark, Idaho Poison Center, 1055 N Curtis Rd, Boise 83706. (208) 378-2159.

May 13-15—**Idaho Academy of Family Physicians—43rd Annual Meeting.** The Coeur d'Alene, Coeur D'Alene. Mon-Wed. Contact: Mrs Irma Sparks, Exec Dir, IAFP, PO Box 175, Boise 83701.

July 25-27—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 15-16—**Southwest Psychiatric Symposium on Substance Abuse.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

March 1-2—**Advances in Internal Medicine.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

March 2—**1991 Wylder Lectures: Pediatric Management of Learning Disorders.** Nursing-Pharmacy Building, University of New Mexico School of Medicine, Albuquerque. Sat. Contact: Marilyn Stark, 7605 Mountain Rd NE, Albuquerque 87110. (505) 265-7431.

March 6-9—**New Mexico Metabolism Symposium.** Quail Ridge Inn, Taos. Wed-Sat. Contact: Lettie Dupuy, Lovelace Medical Foundation, 2441 Ridgecrest SE, Albuquerque 87108. (505) 262-7749.

March 13-14—**Transvaginal Ultrasound.** Marriott Hotel, Albuquerque. Wed-Thurs. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

March 14-16—**24th Annual OB/GYN Postgraduate Update.** Hyatt Regency, Albuquerque. Thurs-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

March 16—**AIDS Update.** University of New Mexico School of Nursing and Pharmacy Auditorium, Albuquerque. Sat. Contact: Marsha VerPloegh, Psychiatric Medical Association, PO Box 26666, Albuquerque 87125. (505) 291-5375.

April 5-6—**Genetics for the Obstetrician.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: Mary R. Boning, Presbyterian Healthcare Services, PO Box 26666, Albuquerque 87125. (505) 841-1225.

April 5-6—**13th Annual Pediatric Cardiopulmonary Update.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

(Continued on Page 232)

TAGAMET® (brand of cimetidine)

See complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Contraindications: *'Tagamet' is contraindicated for patients known to have hypersensitivity to the product*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' (brand of cimetidine hydrochloride) Injection by intravenous bolus*

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy

Reversible confusional states have been observed on occasion, predominantly in severely ill patients

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d dosage of theophylline [Theo-Dur®, Key Pharmaceuticals, Inc.] demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older Data beyond ten days are not available [Note All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.]

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'

A weak antiandrogenic effect has been demonstrated in animals. In human studies, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity

Pregnancy Category B Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to 'Tagamet' There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Lack of experience to date precludes recommending 'Tagamet' for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported Reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population Gynecomastia has been reported in patients treated for one month or longer Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported Increased serum transaminase has been reported Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported Increased plasma creatinine has been reported Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with pre-existing arthritis have been reported rarely Rare cases of polymyositis have been reported, but no causal relationship has been established Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists Reversible alopecia has been reported very rarely*

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Articles

American Travel Deaths in Mexico
Causes and Prevention Strategies

KATHARINE S. GUPTILL, ScD, *Berkeley, California;* STEPHEN W. HARGARTEN, MD, MPH, *Milwaukee, Wisconsin; and* TIMOTHY D. BAKER, MD, MPH, *Baltimore, Maryland*

Presented in part at the Travel and Tropical Medicine Update IV—1990 conference sponsored by the University of Washington School of Medicine, Seattle, May 1990.

About 3 to 4 million Americans travel to Mexico every year, yet their mortality experience has never been analyzed. Fatalities among US travelers to Mexico during the years 1975 and 1984 were examined using a previously unanalyzed data source. The leading cause of death to all US travelers to Mexico was injuries (51%), with 18% of deaths resulting from motor vehicle crashes. Of all travelers' deaths, 37% were due to circulatory diseases and less than 1% were due to infectious diseases. While the proportion of all deaths from motor vehicle crashes was similar for US citizens traveling in Mexico and US residents, travelers had significantly higher proportions of injury deaths due to aircraft crashes and drowning. Injury, rather than infectious diseases, appears to pose the greatest risk of death to travelers to Mexico. Physicians and travel clinics need to place greater emphasis on injury prevention when giving advice to clients traveling to Mexico.

(Guptill KS, Hargarten SW, Baker TD: American travel deaths in Mexico—Causes and prevention strategies. West J Med 1991 Feb; 154:169-171)

Mexico receives about 3 to 4 million American visitors each year.[1,2] This large population includes business men and women, students, retirees, and others who may face different health risks from their counterparts residing in the United States. Each year there are about 400 deaths of Americans in Mexico, half of whom are travelers, yet mortality for US citizens traveling in Mexico has never been examined. Hargarten and Baker in a study of Peace Corps volunteer deaths were the first to describe the deaths of Americans overseas.[3] The objectives of the present study were to establish the cause-specific mortality pattern of these US citizens and to identify high-risk groups for which health interventions may be targeted.

Methods and Sources of Data

United States embassy officials are required to report all deaths of US citizens traveling or residing within their jurisdictions. Death reports are sent to the US Department of State, Division of Passports. These documents are used as proof of death by both the government and the next of kin. The documents are not sent to the National Center for Health Statistics or to state vital records officials. According to the director of the Division of Passports, these records have never been analyzed for cause-specific mortality patterns.

The years 1975 and 1984 were selected for analysis. The year 1975 was the earliest year documents were available, and 1984 was the last year for which the documents were complete. Deaths at age 60 years and above outnumbered those at younger than 60 approximately 5 to 1. A 20% systematic sample was taken of the over-60 deaths and a 100% sample of deaths at younger than 60. The expanded sample was used for all analyses.

Data abstracted from the documents included age, sex, occupation, residing or traveling status, diagnosis, hospital occurrence, and medical certification. Names and original residence in the United States were eliminated to preserve confidentiality. The abstracted data were entered into an IBM 4341 computer and analyzed using the Statistical Package for the Social Sciences (SPSSx). The diagnoses were coded using a condensation of the ninth revision of the *International Classification of Diseases.*[4] Deaths were then grouped into five diagnostic clusters for analysis.

Attempts were made to determine the population of US citizens traveling in Mexico. Insufficient data were available for reliable estimates, so mortality rates for travelers were not calculated. The mortality for US citizens residing in Mexico will be examined separately.

Age- and sex-specific proportional mortality ratios (PMRs) were calculated for US citizens traveling in Mexico. Proportional mortality ratios for US residents were calculated from mortality figures collected by the World Health Organization for 1982.[5] Age- and sex-specific PMRs allowed a direct comparison of the cause-specific distribution of deaths in the two populations. It is important to note that with PMRs, a high proportion of deaths in one category will result in the proportion of another category appearing low regardless of the absolute death rate. In addition, PMRs are influenced by the age and sex distribution of study populations.

From the Department of International Health, Johns Hopkins School of Public Health (Drs Guptill and Baker), Baltimore, Maryland, and the Department of Emergency Medicine, Medical College of Wisconsin (Dr Hargarten), Milwaukee. Dr Guptill is currently with Nutritional Sciences, University of California, Berkeley.

This work was supported in part by Saint Luke's Foundation of Milwaukee, Wisconsin.

Reprint requests to Stephen W. Hargarten, MD, MPH, Assistant Professor, Department of Emergency Medicine, Medical College of Wisconsin, 8700 W Wisconsin Ave, Box 204, Milwaukee, WI 53226.

ABBREVIATIONS USED IN TEXT

CI = confidence interval
PMR = proportional mortality ratio

Results

There were 197 deaths of US citizens traveling in Mexico in 1975 and 199 in 1984. The distribution of deaths by age and cause were essentially the same for the two years: therefore, the years were combined for all analyses. Of the reported deaths, 74% occurred in male travelers. Children younger than 15 years accounted for 12% of the deaths, and adults older than 65 years accounted for 18%.

Cause-specific mortality ratios differed between US citizens traveling in Mexico (travelers) and US citizens living in the United States, with deaths due to injury contributing more to the overall deaths of travelers than deaths due to chronic diseases (Figure 1). Travelers had a lower proportion of deaths due to circulatory diseases (37%; 95% confidence interval [CI], 32% to 42%) and malignant neoplasms (4%; 95% CI, 2% to 11%) than did the US population (49% and 22%, respectively). The cause-specific mortality ratio for deaths due to injury (unintentional, homicide, and suicide) was significantly higher for travelers (51%; 95% CI, 46% to 56%) than for US residents (7%).

The elevated proportion of deaths due to injuries for travelers compared with US residents was consistent across age groups for male travelers aged 15 to 54 (Table 1).

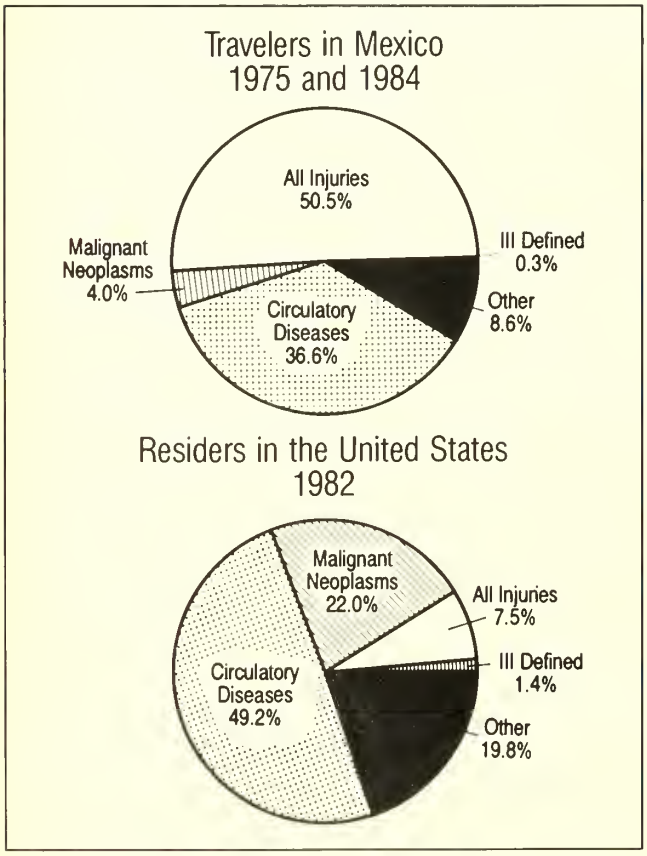

Figure 1.—The proportional mortality ratios are shown for US travelers in Mexico, 1975 and 1984, and for US residents in the United States, 1982 (because of rounding of numbers, the ratios do not add up to 100%). The category "other" includes unspecified medical disorders and infectious diseases.

The types of injury deaths also differed for travelers compared with US residents. Male travelers aged 25 and older did not differ significantly in their proportion of deaths due to motor vehicle crashes compared with their counterparts in the United States (Table 2). Male travelers in this age group, however, had a significantly higher proportion of injury deaths due to aircraft crashes than occurred for US residents. While no differences were seen in the proportion of male deaths due to homicide, suicides made up a significantly smaller proportion of all injury deaths for US travelers when compared with US residents.

Drowning, as a proportion of all male injury deaths, was significantly higher for travelers than for US residents. This difference was found regardless of age. Drowning accounted for 14% (99% CI, 1% to 27%) of injury deaths in the 25 to 34 years age group, 17% (99% CI, 8% to 59%) of the 35 to 55 years age group, and 28% (99% CI, 12% to 43%) of the 45 years and older age group. These proportions compared with PMRs for the same-age US men of 3%, 2%, and 2%, respectively. Although this difference did not reach statistical significance for 25- to 34-year-olds, there was a clear trend.

Age-specific PMRs for male deaths due to circulatory diseases are shown in Table 3. Travelers had lower PMRs

TABLE 1.—*Proportion of Male Deaths Due to Unintentional Injuries, Homicide, and Suicide in US Citizens Traveling in Mexico and in US Residents*

	US Travelers in Mexico			US Residents in the US		
Age Group, years	No.	%	(95% CI)	No.	%	(95% CI)
15-24	26	92	(82-100)	31,376	80	(80-81)
25-34	50	88	(79-97)	35,362	66	(65-67)
35-44	36	83	(71-96)	37,655	34	(33-35)
45-54	58	50	(37-63)	78,007	13	(12-14)

CI = confidence interval

TABLE 2.—*Cause-Specific Distribution of Injury Deaths to Males Aged 25 Years and Older for US Citizens Traveling in Mexico and US Residents*

	US Travelers in Mexico n = 127		US Residents in the US n = 78,667	
Cause	%	(95% CI)	%*	(95% CI)
Motor vehicle crash	24	(20-34)	27	(26-27)
Homicide	12	(6-18)	16	(15-16)
Suicide	4	(3-13)	21	(20-21)
Burns	3	(2-11)	3	(2-3)
Other injuries	26	(18-36)	27	(26-28)
Drowning	20	(13-27)	2	(1-2)
Aircraft crashes	11	(6-16)	4	(3-4)

CI = confidence interval

*Because of rounding, percentages do not add up to 100%.

TABLE 3.—*Proportion of All Male Deaths Due to Circulatory Diseases in US Citizens Traveling in Mexico and US Residents*

	US Travelers in Mexico			US Residents in the US		
Age Group, years	No.	%	(95% CI)	No.	%	(95% CI)
35-44	36	14	(3-25)	37,655	27	(26-28)
45-54	58	31	(19-42)	78,007	42	(41-43)
55-64	82	63	(53-73)	179,322	47	(46-48)

CI = confidence interval

than did US residents until the age of 54 years, although the difference only reached statistical significance for 35- to 44-year-olds. At older ages, this pattern reversed. The PMR for 55- to 64-year-old male travelers is 63% compared with 47% for US residents.

There was only one reported death due to an infectious disease (gastroenteritis) during the years examined in this study.

Discussion

Injuries were the leading cause of death for US citizens traveling in Mexico during 1975 and 1984. Several factors may account for this. First, it is likely that travelers have increased exposure to possible injury. More person-hours may be spent swimming, boating, and traveling when on vacation than when at home. Second, risk-taking behavior may be increased while on vacation. Mixing alcohol consumption with driving or swimming may be more common among vacation travelers than among people who stay at home. Unfortunately, blood alcohol levels, a known risk factor in drowning,[6] were not available from our data source. Third, when an injury does occur, access to adequate emergency medical services may not be as readily available in Mexico as in the US. Unfortunately, the data available will not allow for a determination of the underlying causes of the increased risk.

The PMR for all injuries is particularly high for 15- to 24-year-old males. This high proportion is partially explained by the lower risk of death due to chronic diseases for young people. Males aged 15 to 24, however, should have the same risk of mortality from chronic diseases regardless of traveling status. Thus, the elevated age- and sex-specific PMRs seen for injuries among travelers compared with US residents imply a real, rather than artifactual, increase in risk.

Drowning made up a greater proportion of injury deaths among the travelers than among US residents. The unexpectedly high proportion of injury deaths due to drowning among older travelers (45 years and older) may be a result of the small percentage of deaths due to injuries commonly seen in the US—such as falls. In addition, beaches frequented by travelers are often isolated and unpatrolled, decreasing the chance that those who are drowning will receive prompt and effective rescue and resuscitation. Inexperienced swimmers of all ages should be advised of the greater risks of swimming in unfamiliar waters and the fact that emergency medical services may not be readily available. Travelers should also be advised about the risk of swimming after consuming alcohol.

The PMR for aircraft crashes was significantly elevated for male travelers aged 25 years and older. Unscheduled aircraft flights are a known risk factor for aircraft deaths,[7] but our data source did not specify the types of aircraft crashes. Nonetheless, travelers should avoid unscheduled airplane flights.

Though motor vehicle crashes contributed similarly to injury deaths of US travelers and US residents, Mexico may have special risks and injury patterns. Further study is needed to determine contributions from host, vehicle, and environment, such as alcohol usage, seat belt availability and usage, and the availability of emergency medical services.

United States travelers to Mexico should, whenever possible, use well-maintained, larger cars with seat belts and experienced drivers. Evening driving should be discouraged. Helmets should be worn when riding motorcycles and bicycles.

Deaths due to circulatory diseases and malignant neoplasms occurred in a lower proportion among travelers than among US residents. This may be because healthy, not chronically ill, people travel.

Our study is limited by not including the deaths of travelers to Mexico who return to the United States and die. Further studies are needed to describe this mortality and the morbidity of travelers who return seriously ill or injured. Also, age-specific death rates were not calculated. Additional study is necessary to determine age-specific death rates and describe risk factors for mortality. Better methods of recording the number of travelers to Mexico are necessary before age-specific mortality rates can be determined.

Conclusions

Most American physicians think that their patients who travel to Mexico are at an increased risk from infectious diseases. While this is certainly true for morbidity,[2,8-10] we found that infectious diseases did not significantly contribute to travelers' in-country mortality. The major contributor to deaths for all ages was injury. Travelers' clinics and family physicians should instruct travelers on the risks of motor vehicle and unscheduled aircraft travel and swimming in unfamiliar waters, in addition to the precautions for infectious diseases.

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Articles

Changes in the Relative Frequency of Gastric Adenocarcinoma in Southern California

MAURIZIO BONACINI, MD, *and* JORGE E. VALENZUELA, MD, *Los Angeles, California*

The incidence of gastric cancer is decreasing in most countries of the developed world, but at the Los Angeles County-University of Southern California Medical Center, we diagnosed 99.8 cases of gastric adenocarcinoma per 10^5 discharges in the period 1982 to 1986 as opposed to 62.2 per 10^5 discharges in 1972 to 1976 ($P<.0001$). This change involved primarily Hispanics younger than 30 years of age with 30 cases per 10^5 vs 4.2 cases per 10^5 ($P<.0001$) and whites older than 30 years: 87 cases per 10^5 vs 54 cases per 10^5 ($P<.05$) during 1982 to 1986 and 1972 to 1976, respectively. There was no change in the relative frequency rates of gastric adenocarcinoma among African Americans and Asians. Although these changes do not seem important enough to make the detection of gastric cancer a high-priority public health problem, they should alert physicians working in areas with high Hispanic populations of the relative possibility of the occurrence of gastric malignancy even in young patients. Also, we have found that gastric cancer is still prevalent in whites of low socioeconomic class.

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The overall incidence of gastric cancer in the general population has decreased in the United States and in most other countries,[1] although adenocarcinoma remains the most common neoplasm involving the stomach. In patients younger than 30 years, this diagnosis receives, in general, less consideration because gastric cancer occurs infrequently in young patients. At the Los Angeles County-University of Southern California (LAC-USC) Medical Center, we have observed an increasing number of patients with gastric adenocarcinoma, with surprising high frequency in young patients.

To determine whether this represents a true increase in the relative frequency of gastric adenocarcinoma in the patient population admitted to this medical center, we compared the relative frequency of gastric adenocarcinoma diagnosed during two 5-year periods, 1972 to 1976 and 1982 to 1986, among the patients admitted to our medical center. We identified and characterized cases in patients younger than 30 years.

Patients and Methods

We retrospectively reviewed the discharge summaries of all patients with gastric adenocarcinoma diagnosed during two distinct 5-year periods, between 1972 and 1976 and between 1982 and 1986, as available through the tumor registry files of the LAC-USC Medical Center. Patients were divided in five groups according to their ethnic background: Hispanics, whites, African Americans, Asians, and others, based on race, ethnicity of surname, or place of birth.[2] Also, patients were arbitrarily divided in two age categories—young: younger than 30 years, and old: older than 30 years. We calculated age- and race-specific frequency rates of gastric adenocarcinoma per 100,000 discharges to the LAC-USC Medical Center during the two 5-year periods and analyzed these results using the Poisson distribution.*

*Linda Chan, PhD, assisted with the statistical analysis.

Results

Incidence of Gastric Adenocarcinoma

Between 1972 and 1976 at our institution, 144 patients were diagnosed as having gastric adenocarcinoma; this reflects a relative frequency of 62.2 per 10^5 discharges per 5 years. By contrast, during 1982 to 1986, this same diagnosis was given to 210 patients, a relative frequency of 99.8 per 10^5 discharges per 5 years ($P<.05$) (Table 1).

In addition, there was a change in the ethnic background of patients seen at the LAC-USC Medical Center. The overall number of Hispanics seen in this hospital increased from 63,435 during 1972-1976 to 89,100 during 1982-1986, a 40% increment. Of note, the total number of cases of gastric adenocarcinoma among Hispanics increased from 53 cases or 83.6 per 10^5 discharges per 5 years during 1972-1976 to 101 cases or 113.4 per 10^5 per 5 years during 1982-1986 ($P<.05$). Further analysis of the Hispanic patient population reveals that the increase appears to affect more frequently young patients (younger than 30 years), as 10 cases were diagnosed between 1982 and 1986, or 30 per 10^5 per 5 years, as compared with 1 case diagnosed between 1972 and 1976, or 4.2 per 10^5 per 5 years ($P<.001$). In addition, the incidence of gastric adenocarcinoma among Hispanics older than 30 years increased from 131 per 10^5 per 5 years between 1972 and 1976 to 163 per 10^5 per 5 years between 1982 and 1986, although this did not reach a level of significance.

Even after excluding the Hispanic population, a significant increase in the relative frequency of gastric adenocarcinoma from 54 per 10^5 per 5 years between 1972 and 1976 to 89.8 per 10^5 per 5 years between 1982 and 1986 ($P<.0001$) was observed in LAC-USC patients (Table 1). Most of these cases were in whites older than 30 years (53.9 per 10^5 during 1972-1976 vs 87 per 10^5 during 1982-1986 [$P<.05$; Table 2]). There was no change in the gastric cancer rate among young white patients.

A frequency rate of gastric adenocarcinoma higher

From the Department of Medicine, Division of Gastroenterology, University of Southern California School of Medicine, LAC-USC Medical Center, Los Angeles.
Reprint requests to Jorge E. Valenzuela, MD, Department of Medicine, Division of Gastroenterology, USC School of Medicine, 2025 Zonal Ave, Los Angeles, CA 90033.

among Asians than among the other groups was expected, but we did not find a significant change between the two 5-year periods analyzed (Table 2). Also, no changes in the relative frequency of adenocarcinoma of the stomach were detected in African Americans seen at LAC-USC Medical Center.

Features of Gastric Adenocarcinoma in Young Patients

There were 10 young Hispanics and 2 non-Hispanics with the diagnosis of adenocarcinoma of the stomach between 1982 and 1986. Their mean age was 25.2 years (range 19 to 29 years) and the male-to-female ratio was 1:1. Their clinical presentation was not particularly remarkable, with abdominal pain and vomiting as the most common symptoms; physical findings were scarce. Esophagogastroduodenoscopy was carried out in all patients and was diagnostic with abnormal findings in all of them, except for one case that was diagnosed at the operation. Nine patients underwent surgical resection. Two of these patients died within 18 months of the diagnosis. Another patient was lost to follow-up. Two of the remaining patients are alive and well (without evidence of disease) 16 and 28 months following resection. Four patients received adjuvant chemotherapy with fluorouracil, doxorubicin (Adriamycin) hydrochloride, and mitomycin. Three of these patients died within two years, and one is alive and well six years after surgical resection.

Two other patients received radiation therapy and chemotherapy and died 2 and 26 months, respectively, after the diagnosis. One patient was treated with radiotherapy alone and died 5 months later.

Discussion

Although the incidence of gastric adenocarcinoma has decreased in the United States and in Western Europe[1] and is decreasing in Japan,[3] it still remains an important public health problem because of its poor survival rate. An aggressive approach with early diagnosis has produced a drastic change in the prognosis of gastric cancer in Japan, with a five-year survival higher than 80% in patients with "early" cancer confined to the mucosa or submucosa.[4] A similar program in the US does not seem to be cost-effective. In this report we review our experience at the LAC-USC Medical Center where we observed a relatively greater frequency of cases of gastric adenocarcinoma in recent years. This increase is seen particularly among young Hispanics and among whites older than 30 years (Table 1). The LAC-USC

TABLE 1.—*Age- and Race-Specific Relative Frequency Rates per 100,000 Discharges for Gastric Adenocarcinoma, 1972 to 1976 and 1982 to 1986*

		1972-1976			1982-1986			
Ethnic Group	*Age Group, yr*	*Cases, No.*	*Patients, No.*	*Rate*	*Cases, No.*	*Patients, No.*	*Rate*	*Relative Risk**
Hispanic	<30	1	23,875	4.2	10	33,386	30.0	7.2†
	≥30	52	39,560	131.4	91	55,714	163.3	1.2
	Total	53	63,435	83.6	101	89,100	113.4	1.4‡
Non-Hispanic	<30	1	43,720	2.3	2	33,804	5.9	2.6
	≥30	90	124,180	72.5	107	87,515	122.3	1.7†
	Total	91	167,900	54.2	109	121,319	89.8	1.7†
Total	<30	2	67,595	3.0	12	67,190	17.8	5.9†
	≥30	142	163,740	86.7	198	143,229	138.2	1.6†
	Total	144	231,335	62.2	210	210,419	99.8	1.6†

*Poisson distribution was used to determine the *P* values for the <30 group, and Fisher's exact test was used to determine the *P* values for the ≥30 group.
†Significant at *P* <.0001.
‡Significant at *P* <.05.

TABLE 2.—*Age- and Race-Specific Relative Frequency Rates per 100,000 Discharges for Gastric Adenocarcinoma, 1972 to 1976 and 1982 to 1986*

		1972-1976			1982-1986			
Ethnic Group	*Age Group, yr*	*Cases, No.*	*Total No. of Patients Discharged*	*Rate*	*Cases, No.*	*Total No. of Patients Discharged*	*Rate*	*Relative Risk*†*
Hispanic	<30	1	23,875	4.2	10	33,386	30.0	7.2†
	≥30	52	39,560	131.4	91	55,714	163.3	1.2
	Total	53	63,435	83.6	101	89,100	113.4	1.4‡
White	<30	1	25,195	3.8	0	16,366	0.0	0.5
	≥30	39	72,308	53.9	35	40,249	87.0	1.6‡
	Total	40	97,503	40.7	35	56,615	61.8	1.5‡
African American	<30	0	16,499	0.0	1	15,028	6.6	2.2
	≥30	41	48,410	84.7	35	38,940	90.0	1.1
	Total	41	64,909	63.2	36	53,968	66.7	1.1
Asian	<30	0	676	0.0	1	1,538	65.0	0.9
	≥30	9	1,767	509.3	37	5,384	687.2	1.4
	Total	9	2,443	368.4	38	6,922	549.0	1.5
Other	<30	0	630	0.0	0	872	0.0	0.7
	≥30	1	1,695	59.0	0	2,942	0.0	0.2
	Total	1	2,325	43.0	0	3,814	0.0	0.2

*Poisson distribution was used for <30 group. Used 0.5 adjustment when zero.
†*P* <.0001.
‡*P* <.05.

Medical Center serves the medical needs of lower socioeconomic classes in the Los Angeles area where the Hispanic population has grown noticeably. Hispanics now represent more than 40% of the admissions to the LAC-USC Medical Center. One possibility to explain the increased incidence of gastric adenocarcinoma found in this population may be the more widespread use of esophagogastroduodenoscopy in recent years. Although this factor would help in the earlier diagnosis of gastric cancer, the progressive nature of this disease and the fact that we selected the criterion of the discharge diagnosis and not the endoscopic diagnosis makes this possibility less likely.

Although the total number of cases of gastric adenocarcinoma in Asians increased from 9 (1972 to 1976) to 38 (1982 to 1986), this does not represent a higher frequency, as the total number of Asians discharged from LAC-USC Medical Center has tripled during the same period. Race-specific rates for gastric adenocarcinoma in the general population are high for Asians, with the highest rates found in Korea and Japan.[5,6] In China and Singapore, also, death rates from gastric cancer are higher,[6-8] whereas in Thailand and the Philippines they are lower than those in the US.[7] In this study we have confirmed the high frequency of gastric adenocarcinoma among Asians, but we have not observed a significant increase in the relative frequency rate of gastric adenocarcinoma in this ethnic group during the two periods.

The second highest rates of gastric cancer in the world are found in Hispanics. Central and South American countries such as Chile, Costa Rica, Argentina, and Colombia have reported high death rates for gastric cancer in the general population.[7] By contrast, data from Ecuador, Guatemala, Honduras,[7] and Mexico[9] show rates comparable to or lower than those of the United States. Unfortunately, these last data may have underestimated the true incidence of gastric adenocarcinoma in these countries. For example, in the Los Angeles area, where most Hispanics are from Mexico and Central America, Spanish-surnamed patients have a twice higher incidence rate for gastric adenocarcinoma than those not having Spanish surnames.[10] The difference in incidence between immigrants and residents in their native country may represent a bias in the selection, including reasons for immigration, socioeconomic status, and the like. Of interest, it has been noted that first-generation Japanese immigrants to the US have an incidence of gastric cancer similar to that of the region where they spent their early years. The descendants of the same immigrants by contrast show an incidence similar to that of Native Americans.[11]

Thus, it appears that the increase in the total number of cases of cancer seen at our institution mainly reflects the increasing proportions of Hispanics and Asians that come to our medical center. Of great interest is the high number of young Hispanics found to have gastric adenocarcinoma. This is in agreement with a recent report from the University of California, Los Angeles, Medical Center showing that young patients (younger than 36 years) represent a higher percentage of gastric carcinoma in Hispanics (18%) than in non-Hispanics (2.8%).[12] Our data not only show similar percentages (10% vs 1.8%) but also document a significant increase in the relative frequency of gastric adenocarcinoma in young Hispanics from 1972-1976 to 1982-1986. Taken together, the study from UCLA and the present report suggest that the high frequency of gastric cancer and the findings among young Hispanics represent a more generalized problem in southern California.

An unexpected finding is the increased relative frequency of gastric adenocarcinoma in whites older than 30 years, which seems in contradiction with current epidemiologic data from the Western world as a whole. The reasons for this increase are not entirely clear. We see in our medical center a selected white population, mostly from low socioeconomic class, in itself a risk factor for gastric adenocarcinoma. Changes in the availability of health care resources may have resulted in an increased referral of these patients to our institution. In addition, more whites may have migrated from Europe, where most countries have substantially higher rates than the US.[7] High-risk pockets exist even within this country, the highest rates being seen in whites in Hawaii and the lowest in Atlanta, Georgia.[1] Thus, we may have witnessed an increased migration of whites from states or countries with high rates of gastric cancer.

In conclusion, more cases of gastric adenocarcinoma are being seen in our patient population at the LAC-USC Medical Center. An increased number of immigrants from high-risk areas—Central and South America, Korea, Japan, China—only partly explains this rise. Higher frequency rates in young Hispanics and whites older than 30 years are not readily explained. Further epidemiologic investigations are needed to determine if our experience merely reflects a particular pattern of referral from high-risk populations or truly represents an increased incidence of gastric adenocarcinoma in the population at large.

Because the key to a better prognosis in gastric adenocarcinoma is an early diagnosis, we recommend a more aggressive diagnostic approach in patients with an ethnic background at higher risk of gastric adenocarcinoma, including young Hispanic patients. Our observation should alert practicing physicians in all areas of the US where a higher proportion of Hispanic and Asian patients is seen. Our findings, on the other hand, do not suggest that an aggressive screening program be implemented.

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Articles

Health Resources Management and Physician Control in a San Francisco, California, Hospital

ALAN H. ROSENSTEIN, MD, MBA, *and* MARGARET M. STIER, *San Francisco, California*

The continued escalation in health care spending has caused money to become an increasingly limited resource, which may eventually affect the ability of health professionals to provide complete health care services. Health care payers have stressed efficiency and the appropriateness of health care measures and are putting greater financial pressures on health professionals by making them more accountable for services provided. Hospitals and physicians must take a more active role in monitoring health care delivery and work together to improve performance efficiency. Efficiency can be gained through a comprehensive program that emphasizes high-quality care and the effective use of health care resources. The Health Resource Management Program is a model for carrying out this function that integrates data analysis and physician input and education.

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As health care spending continues to escalate, health care purchasers will continue to pursue alternatives designed to reduce their health care burden. In the early 1980s, the first round of alternatives was introduced with measures aimed at reducing hospital expenditures by direct utilization controls and reimbursement limitations. Government-mandated payments by diagnosis (Medicare) and payments per diem (Medi-Cal) were the new payment buzzwords in the early 1980s. In 1980 $248 billion was spent on health care services. In 1985 health care spending nearly doubled to $423 billion, consuming almost 10% of the Gross National Product.

Following the federal government's lead, the next wave of alternatives came from the industrial sector, which marked the beginning of the managed care era. Health maintenance organizations, preferred-provider organizations, exclusive-provider organizations, and individual practice associations became the buzzwords of the late 1980s. If direct controls could not reduce health care spending, maybe the establishment of a retail-like competitive marketplace would do better. In 1989 more than $600 billion was spent on health care services, consuming nearly 12% of the Gross National Product.

The decade of the 1990s brings us the third stage of alternatives to reduce health care spending. Health care purchasers have now begun to take a more active role in scrutinizing the actual process and outcome of health care delivery, demanding to know the indications and justifications for health care actions and interventions. Insurance companies have begun to deny payments for medically unnecessary services or to retrospectively demand that fees for unwarranted care be repaid. A new medical enterprise has sprouted of corporations whose sole function is to "second-guess" physicians' orders and hospital-related services through direct chart reviews and bill audits. These companies contract directly with health-care purchasers in an effort to reduce payments for unsubstantiated charges (A. Miller, "Second-Guessing Doctor's Orders," *Newsweek*, May 23, 1988, pp 44-45; S. Findlay, "Looking Over the Doctor's Shoulder," *U.S. News & World Report*, January 30, 1990, pp 70, 73). As these claims analysis and data information systems proliferate, more and more insurance payers are leaning toward selective contracting with "more efficient" health care providers.[1] Efficacy, efficiency, appropriateness, and accountability have become the buzzwords of the 1990s.

With some predictions that health care spending will reach the $1.5 trillion mark by the year 2000, money will become even more of a limited resource, and more drastic alternatives are predicted for the future. At one end of the spectrum are the proponents of universal health insurance who feel that the only way to control health care costs is to nationalize the entire system. At the other end are the proponents of health care rationing who favor a system of direct limitations on health care access. The state of Oregon has already instituted such a system for its indigent population wherein payment coverage for medical services is limited, based on a ten-point medical priority system (M. Cannel, D. Wyss, "Rationing Medical Care," *Time*, May 15, 1989, p 54). California had considered its own rationing system for Alameda County but subsequently decided against implementing it.[2]

With this information in mind, let us focus our attention on the new priorities in health care. With money becoming more of a limited and restricting resource, physicians' objectives are to take the lead in managing health care resources in the most effective manner possible in an effort to maintain patient access and provide appropriate cost-efficient, high-quality care.

We present an example of how this can be accomplished in the hospital sector. Using hospital economics as a measurement guideline, we can see how changes in behavior can affect financial performance. While improved financial per-

From Medical Resource Management, Children's Hospital of San Francisco, California.

Reprint requests to Alan H. Rosenstein, MD, MBA, Director of Medical Resource Management, Children's Hospital of San Francisco, 3700 California St, San Francisco, CA 94118.

formance can be attributed to several different factors, in the context presented in this article, it will be used as an indicator of greater efficiency of care.

Local Hospital Effects

Utilization restrictions, reimbursement limitations, and managed care alternatives have considerably affected the local San Francisco health care system. With 11 hospitals left in a small geographic area, and with a growing dominance of the Kaiser-Permanente system (approaching 30% of the northern California market), all hospitals are suffering the consequences of reduced market share and dwindling inpatient revenues. Over the past ten years, several hospitals have been forced to close or to otherwise lose their autonomy through various affiliations or mergers, and this trend is likely to continue. In an effort to maintain financial viability, hospitals have had to take serious steps to maintain revenues. By looking at the economic equation,

$$\text{Net Income} = \text{Revenues (Price} \times \text{Volume)} - \text{Expenses}$$

the reasons why hospitals are in such a precarious financial situation become apparent. Hospitals are limited in their opportunities to increase total revenue by utilization restrictions and to increase volume by competition. Reimbursement limitations and other forms of discounted care limit the ability to increase prices. A reduction in expenses has primarily been approached by trying to reduce overhead, limiting full-time-equivalent employees, or instituting various cost-containing programs. The only approach left is to reduce expenses by improving the efficiency of operations. The efficiency of operations can be improved through the various components of health care delivery. Admissions, discharge, lengths of stay, diagnostics, and therapeutics are all various components under physicians' control. Improving efficiency in these areas can have a profound effect on the bottom line. The following example will explain this concept in more detail.

Case Example

Children's Hospital of San Francisco is a 467-bed nonprofit, acute care adult and pediatric hospital located in metropolitan San Francisco. Like most hospitals in the city, most of its patients are covered by an insurance payment system that pays something other than full fee-for-service charges (Figures 1 and 2). In fact, 80% of the patients are paid either by the diagnostic group (Medicare), per-diem payments (Medi-Cal [California's Medicaid], health plan), capitation, or other forms of negotiated fee-for-service discounted plans. When the total charges are compared with the actual amount of monies received, there is a substantial discrepancy between the two categories. This discrepancy can be called "contractual deductions," and for different hospitals this could add up to as much as 30% to 60% of charges depending on the payer mix. A contractual deduction of 50% means that the hospital collects only 50 cents on each dollar charge. This implies that for most payer categories, it is in the hospital's

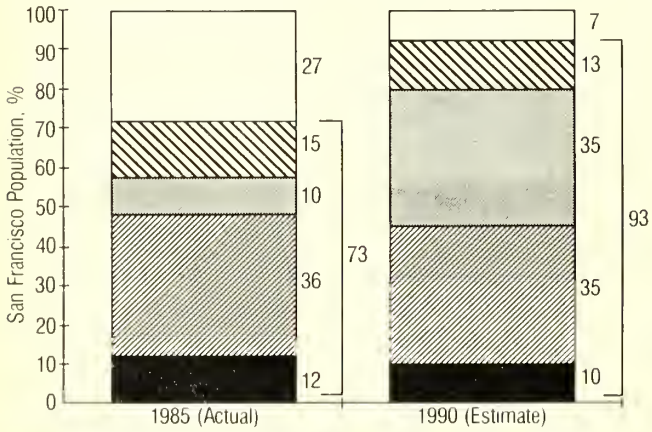

Figure 1.—The graphs show the shift to managed care in the San Francisco Bay Area, 1985 to 1990 (from J. X. Reynolds and Company, *Marketplace Analysis*, July 30, 1986, San Francisco, California). ▯ = fee-for-service, ⧅ = Medicare (excludes Medicare population that will shift to capitated programs [PPOs/HMOs]), ▨ = preferred-provider organization (PPO) or other health maintenance organization (HMO) (includes 20% of Medicare patients who will shift to capitated programs [PPOs/HMOs]), ▨ = Kaiser-Permanente, ■ = Medi-Cal

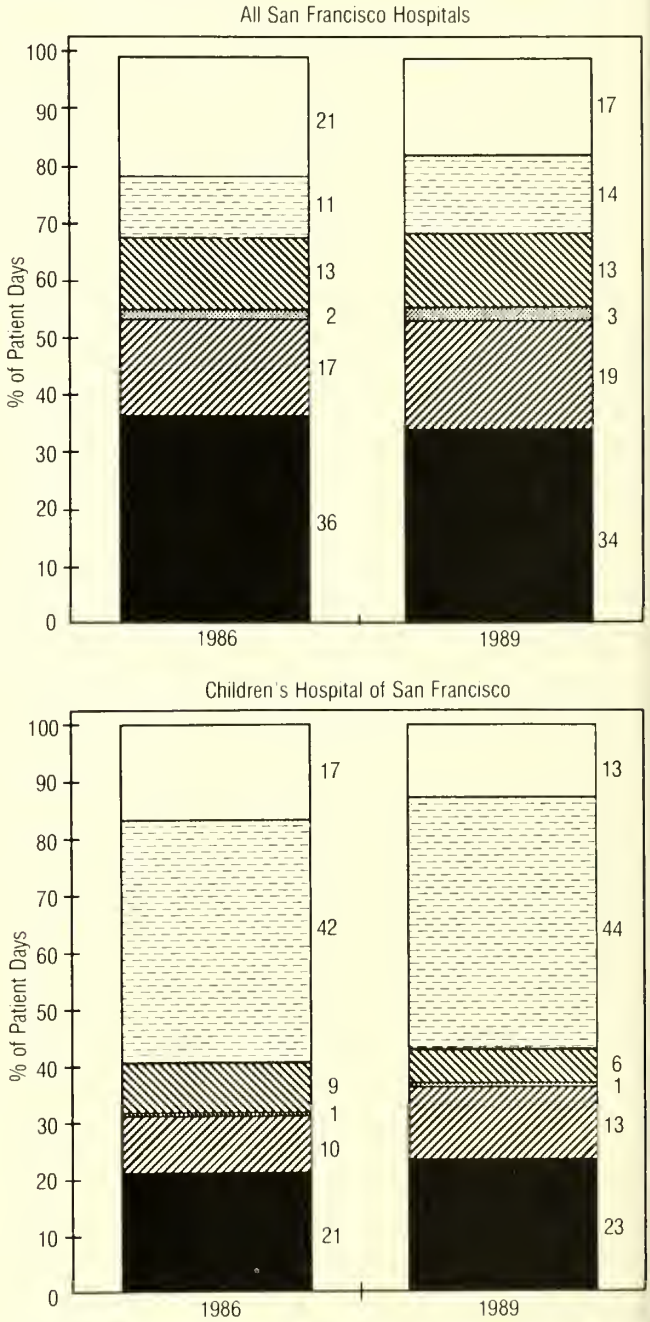

Figure 2.—The graphs show the payer mix trends in San Francisco only, based on patient days (from the West Bay Hospital Patient Discharge Study, 1986 and 1989, Children's Hospital of San Francisco Case-Mix Library. ▯ = commercial, ▤ = health maintenance organization or preferred-provider organization, ⧅ = other, ▩ = medically indigent adults, ▨ = Medi-Cal, ■ = Medicare

best financial interest to provide only the minimal services necessary in the most expedient manner possible to maximize the potential for financial gain.

Unfortunately from a purely economic perspective, hospital financial incentives are often different from physicians' financial incentives because physicians are still predominantly paid by the customary fee-for-service system. Table 1 shows that a hospital is at various levels of financial risk (risk of nonpayment for services provided) for different payer categories if an admission is "not approved" (Medicare, Medi-Cal, other), if the lengths of stay are long (Medicare, capitation), if there are "unapproved" hospital days (Medi-Cal), or if a high intensity of resources is used (Medicare, Medi-Cal, capitation). On the other hand, physicians are at minimal risk for services provided because most of the insurance categories still reimburse physicians on a fee-for-service basis and, for the most part, physicians still get reimbursed for services provided even when hospital payments have been denied.

It is difficult to ask physicians to treat hospital inpatients differently according to their insurance status. Our approach has been to try and treat all patients as efficiently and effectively as possible in the interests of high-quality, cost-efficient care. The medical resource management model described herein reflects efforts to establish a mechanism to monitor patient care activities in an attempt to improve their efficiency. We have translated measurements from quality control, utilization review, and resource consumption into economic indicators as a way to measure and compare performance.

TABLE 1.—*Economic Incentives by Payer Mix*

Economic Incentive	*Admission*	*Length of Stay*	*Resources Used*
For Hospitals			
Full charge*	+	+	+
Discounted charges†	+?	+?	+?
Payment per case‡	+?	–	–
Payment per diem§	+?	+??	–
Capitation‖	–	–	–
For Physicians			
Full charge*	+	+	+
Discounted charges¶	+	+	+
Payment per case#	+?	+	+
Payment per diem**	+	+?	+?
Capitation‖††	–	–	–

+ = desirable/increase, – = undesirable/decrease

*Reimbursed for services provided. For physicians, fee-for-service.

†Preferred-provider organizations (PPOs): Reimbursed on percentage of charges; the question is whether discounted reimbursement is enough to cover costs.

‡Prospective payment (diagnosis-related groups [DRGs]): Fixed payment, with the emphasis to do less; the question is that it is subject to "admission approval."

§Medicaid: Paid by the day, with the emphasis to do less; the questions are that it is subject to "admission approval" and payment may be only for "medically necessary" days.

‖Payment per enrollee (health maintenance organizations [HMOs]): Money is paid "up front," with incentive to do less.

¶(PPOs) Same incentives as for fee-for-service.

#Medicare (DRGs): Physicians are reimbursed for services provided; the question is that Medicare may deny payment for unnecessary services.

**Medicaid: Physicians are reimbursed for services provided; the question is that Medicaid may deny payment for unnecessary services.

††Physicians may be on fee-for-service reimbursement with hospital on capitation.

Hospital Model

The medical resource management model draws information from quality assurance, infection control, and utilization management and coordinates this information with input from nursing personnel, department managers, administrators, and physicians into one centralized program designed to produce high-quality, cost-effective care. Regarding quality assurance and infection control, the emphasis is to identify unwanted trends or variances in medical care that substantially affect medical quality and then to develop strategies to reduce these events through a process of monitoring and control. Using postoperative infections as an example, the model involves taking proactive measures to reduce the incidence of postoperative pneumonias, surgical wound infections, or urinary tract infections that not only improve quality of care but also save the additional costs of treating these complications, which can range between $3,000 and $30,000, depending on the severity of the problem.[3] Regarding utilization management, assuring the necessity of admissions, expediting treatment plans, and reducing lengths of stay can have a profound effect on financial performance. Reducing lengths of stay by even one day can save a hospital as much as $1,000 per patient in nonreimbursed charges. Utilization management can be extended to include monitoring the use of ancillary resources. Ancillary resources include laboratory services, pharmacy, radiology, nuclear medicine, respiratory therapy, physical therapy, central supply, or any other service ordered by a physician as an additional item. In financial terms, these resources can be referred to as variable services—to distinguish them from the fixed services associated with hospital room and nursing—and, depending on the type of admission, can account for as much as 50% of total hospital charges. Considerable efficiency can be gained by maximizing the efficient use of such resources.

Case Study

The goal of developing such a program is to monitor specific hospital-related medical services with the overall intent of improving efficiency of care. Each hospital will want to focus on areas that are most appropriate for its own individual needs. Priorities may be set by analyzing high-

TABLE 2.—*Diagnosis-Related Group (DRG) Summary Averages, 1987 (Before Study)*

				Charge/Patient, $								
*DRG No.**	*Patients, No.*	*Average Length of Stay, days*	*Average Age, years*	*Gross Revenue*	*Room*	*Pharmacy*	*Laboratory*	*Surgery*	*Physical Therapy*	*Central Services*	*X-Ray*	*Other Ancillary Charges*
209	129	10.56	66	17,756	5,878	1,036	733	7,381	633	1,158	267	670
210	48	11.71	71	16,302	6,762	1,340	1,492	3,186	586	1,085	798	1,053
211	15	8.93	35	11,022	4,906	973	397	2,953	379	795	372	247
212	19	4.68	9	7,421	2,693	539	263	2,985	89	319	279	254
Total/Average	211	10.18	60	16,016	5,723	1,056	839	5,716	556	1,040	396	690

*DRGs 209 through 212 refer to Major Joint Procedures.

volume or high-cost admissions, looking at categories by profit or loss, or focusing attention on special projects or known areas of concern. In our case, we decided to do a focus study on diagnosis-related groups (DRGs) 209 to 212, Major Joint Procedures.

Table 2 lists DRGs 209 to 212 and summarizes the 1987 prestudy results according to charges derived in the different ancillary resource centers. The population studied includes all payer categories but is presented under the DRG categorization for convenience and familiarity. We focused on hospital charges rather than costs because charges are the standards for reporting and charge information is more readily accessible. While we appreciate the discrepancy between costs and charges, charges still give us a fair representation of resource consumption, and we can avoid the issue of justifying hospital costs. Table 3 summarizes the same results by individual physicians where behavior patterns can be compared and analyzed on a physician-to-physician basis.

TABLE 3.—*Physician Summary Averages, 1987*

				Charge/Patient, $								
Attending Physician	*Patients, No.*	*Average Length of Stay, days*	*Average Age, years*	*Gross Revenue*	*Room*	*Pharmacy*	*Laboratory*	*Surgery*	*Physical Therapy*	*Central Services*	*X-Ray*	*Other Ancillary Charges*
1	2	9.00	70	17,444	4,924	807	950	7,337	618	1,076	218	1,514
2	15	8.87	59	15,881	5,042	1,157	896	6,170	545	1,000	487	584
3	2	6.00	31	6,256	3,299	395	84	2,187	0	245	0	46
4	10	10.80	69	17,416	6,153	1,397	886	6,342	599	1,176	255	608
5	6	10.00	77	15,451	5,909	991	1,337	4,168	574	842	774	856
6	51	10.27	64	17,310	5,652	990	771	7,151	610	1,196	288	652
7	14	9.21	59	12,964	5,155	846	615	4,085	497	819	436	511
8	9	16.44	66	22,693	9,251	1,635	1,224	5,924	1,109	1,506	789	1,255
9	15	10.73	62	19,050	6,261	1,357	1,072	7,106	519	1,739	299	697
10	1	6.00	78	9,135	3,300	161	414	3,091	336	552	810	471
11	28	9.29	57	14,297	5,111	860	587	5,456	516	937	287	543
12	14	6.86	15	11,292	4,039	750	388	4,908	210	498	305	194
13	12	9.50	62	14,312	5,284	972	802	4,754	480	836	522	662
14	3	14.33	68	20,267	7,937	1,063	1,785	6,223	637	1,152	593	877
15	11	11.18	62	16,227	6,150	1,148	719	5,186	505	894	474	1,151
16	7	13.57	83	19,779	8,316	1,628	1,959	3,167	775	1,231	906	1,797
17	8	11.13	62	13,903	6,075	1,277	1,007	3,483	607	514	382	558
18	1	12.00	74	19,411	7,425	916	1,629	5,479	588	1,933	367	1,074
19	1	11.00	80	15,728	5,775	481	590	7,199	511	832	0	340
20	1	5.00	42	9,184	3,015	505	486	4,294	231	301	173	179
Total /Average	211	10.18	60	16,016	5,723	1,056	839	5,716	556	1,040	396	690

TABLE 4.—*Surgery Summary of Diagnosis-Related Group 209, Hip and Knee Procedures, by Attending Physician*

			Surgery Charges Breakdown, Charge/Patient, $				
Physician	*Patients, No.*	*Total Surgery Charge/Patient, $*	*Surgery*	*Anesthesia*	*Recovery Room*	*Prosthesis*	*Tray/Pack/ Supply*
1	2	7,337	2,229	423	575	3,278	831
2	10	7,285	3,044	438	399	2,694	711
3	0	0	0	0	0	0	0
4	9	6,581	2,421	398	328	2,612	821
5	1	6,382	1,720	351	361	3,132	818
6	42	7,949	3,039	448	436	3,109	918
7	6	5,882	1,838	360	255	2,573	856
8	5	7,441	2,657	407	403	3,103	871
9	12	7,912	2,301	458	287	3,501	1,366
10	0	0	0	0	0	0	0
11	18	6,999	2,619	379	374	2,782	845
12	4	9,392	4,464	464	346	3,565	553
13	6	6,759	2,468	353	223	2,902	813
14	2	8,034	4,588	433	336	3,810	772
15	7	6,375	1,830	340	424	2,946	834
16	1	6,418	2,055	445	305	2,950	663
17	2	6,933	2,542	320	347	2,935	789
18	1	5,479	1,540	220	401	2,675	643
19	1	7,199	2,263	370	442	3,770	354
20	0	0	0	0	0	0	0
Total/Average	129	7,381	2,719	414	378	2,985	886

This macro-analysis can help pinpoint areas for further study. Each department was analyzed in more detail to see if efficiency could be gained by improving performance in these areas. In the pharmacy, efficiency could be gained by using more cost-effective antibiotics and analgesics. In the laboratory, efficiency could be gained by more effective ordering patterns that encouraged the use of more standard laboratory profiles or substituting less costly tests (for example, hemogram vs a complete blood count, blood type and screen vs blood type and cross) when clinically acceptable. The greatest area for improvement was in the surgery department. Table 4 analyzes DRG 209 (Hip and Knee Procedures) and provides a more comprehensive look at the different components that make up the surgery center. Each of these components was studied in detail in an effort to determine where to focus our efforts to improve efficiency in care. The biggest ticket item was in the prosthesis charge per patient. By analyzing how prostheses are used, we found that efficiency could be gained by encouraging the use of standard rather than custom-ordered prosthetic devices. Table 5 lists charges for total hip and knee prostheses, in which the differences can amount to several thousand dollars in hospital charges. Noting the large amount of physician variance in this area, we found that encouraging a more standard use of prosthetic devices produced a substantial financial savings without a compromise in the overall quality of care.

TABLE 5.—*Orthopedic Prosthesis Comparison*

Cost Range	Cost of Prosthesis, $	
	Total Hip	Total Knee
Low range	2,350	2,350
High range	3,100	2,950
Revision	3,400	3,650
Custom	5,000-6,000	5,000-6,000
Plus Additional Costs for Custom Work		
Usage fee	250	250
Freight	100	100

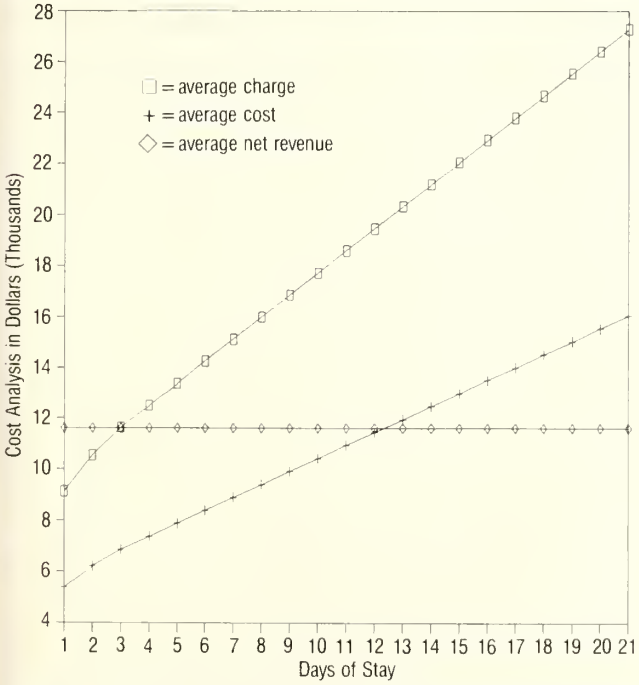

Figure 3.—The graph shows the break-even analysis for a total hip procedure (diagnosis-related group [DRG] 209), January 1, 1987, through December 31, 1987. Average length of stay for DRG 209, 10.6 days; average total charge, $17,756; average operating cost, $10,451; average net revenue, $11,612; average fixed charge per case, $5,878 (33%); average surgical charge per case, $7,381 (42%); average variable charge (excluding surgery) per case, $4,497 (25%).

The cumulative results from DRG 209 are plotted in Figure 3. This graph is intended to illustrate the potential financial impact of the suggested interventions. Although the graph describes results for DRG 209, all charges are the same regardless of insurance classification. The average net revenue is that received from all payer classes and is plotted as a straight line. The average charge line indicates the total cumulative charges for medical services. The average cost line indicates the actual cumulative cost to the hospital of providing such services. The contractual loss portion indicates the difference between total charges and net revenue received. Notice that after day 2, the total charges exceed actual reimbursement. The net profit portion indicates the difference between actual costs and revenues received. Notice that the hospital continues to make a profit through day 11. Profit can be maximized by discharging patients before day 11, which moves the cost line to the left. (In our hospital, discharge can be expedited because there is an on-site skilled nursing facility.) Profit can also be maximized by improving the efficiency in which services are ordered, which extends the net profit area by lowering the average cost line toward the baseline.

These are but a few examples of how this type of process has been applied to improve efficiency in the Orthopedic Department. An analysis of other medical departments and services has shown similar results.[4]

Physician Involvement

For the program to work, physicians must actively participate. Although the health care payers want to reduce costs and eliminate the waste and nonessential components of medical care and the hospitals at financial risk want to improve their efficiency in health care operations, it is physicians who have the ultimate responsibility for providing ongoing quality medical care. We have taken the approach of actively involving staff physicians by encouraging their input and recommendations early in the process.

The resource management program involves a five-step process. The first step is the information-gathering and data-analysis phase, looking at the data as they relate to the specific needs of an individual hospital and selecting appropriate areas for study. This leads to the second phase, which requires the identification of priorities and the setting of goals and objectives appropriate to accomplish the desired tasks. The third step involves the presentation of the data to the target group. With physicians as the primary target group (attending physicians and house staff), all the pertinent information is shared with the group and physician participation and involvement are actively encouraged in an effort to help develop appropriate alternatives and guidelines for improving efficiency in care. The fourth step is the educational component, and for the physician group the key lies in physician-physician interaction and education. Many of the objectives outlined can be achieved by simply providing physicians the information and encouraging behavioral change through peer group interaction and the exchange of ideas. Education is conducted in a structured, ongoing manner. Vehicles for

education include grand rounds, department meetings, and a regular series of lectures on economics offered to both residents and attending staff. These efforts are reinforced through individual discussion. It is not enough simply to describe the merits of good efficient care; constant interaction, follow-up, and education are required to produce the desired results. Other groups who also benefit from the education process include nursing, administration, department managers, and other interested hospital personnel. The fifth step is to monitor the results and revise accordingly.

The overall goal of the program is to share information, encourage input, and develop alternatives for improving the efficiency of care. The concept was developed from the perspective that cost-efficiency, efficacy, and high quality of care go hand in hand. Efficiency means not doing more and not doing less than is clinically warranted, and quality is gained by not subjecting patients to unnecessary medical interventions. The program has the benefit of responding to the demands of the "everybody-else-who-is-looking-over-our-shoulders" phenomenon but also provides an opportunity to develop internal controls over the system rather than reacting to externally developed priorities. From a more global perspective, physicians need to take a more active role in recognizing the importance of the efficient allocation of resources, in the interests of having more resources remain available for total patient care.

Physician Behavior

As mentioned earlier, physician participation is the key to the program's success. Because it is physicians who decide which tests to do, the first goal is to improve physician behavior. For many reasons, physicians tend to order a lot of services. In the interests of providing high-quality care, they have been trained throughout medical school and residency programs in a philosophy that equates quantity with quality, and they like to use all the resources at their disposal before reaching a final diagnosis. Kassirer calls this the never-ending quest for diagnostic certainty.[5] If it costs $500 to reach a diagnostic confidence level of 95%, can we continue to afford to spend an additional $500 to increase the diagnostic confidence level to 96%? Other reasons for ordering large quantities of tests include the lack of economic incentives for efficiency propagated by the fee-for-service reimbursement system and defensiveness in reaction to the fear of malpractice suits. Even with all these obstacles, there is still room for improvement.

Several recent studies have indicated that more than $125 billion is spent each year on "wasted" medical services

TABLE 6.—*Orthopedic Diagnosis-Related Group (DRG) Financial Trend Analysis of an Inlier Population,* 1987 and 1988*

Population and Services	Hospital Charge 1987	Hospital Charge 1988†	% Change From 1987
Total Population			
Patients, No.	164	187	14.0
Average length of stay, d	10.1	8.7	−13.9
Average age, yr	64	70	
Average charge per patient, $			
Total gross revenue	16,107	15,145	− 6.0
Pharmacy	1,051	937	−10.8
Surgery	5,771	5,926	2.7
Laboratory	985	858	−12.9
Physical therapy	564	521	− 7.6
Central service	1,027	856	−16.7
X-ray	398	408	2.5
DRG 209 Major Joint Procedure			
Patients, No.	117	116	− 0.9
Average length of stay, d	10	8.5	−15.0
Average age, yr	66	67	
Average charge per patient, $			
Total gross revenue	17,188	16,513	− 3.9
Pharmacy	958	956	− 0.2
Surgery	7,377	7,725	4.7
Laboratory	835	711	−14.9
Physical therapy	602	559	− 7.1
Central service	1,140	896	−21.4
X-ray	247	242	− 2.0
DRG 210 Hip/Femur‡			
Patients, No.	30	37	23.3
Average length of stay, d	10.5	9.4	−10.5
Average age, yr	72	82	
Average charge per patient, $			
Total gross revenue	13,721	13,972	1.8
Pharmacy	963	1,012	5.1
Surgery	2,775	2,929	5.5
Laboratory	1,283	1,339	4.4
Physical therapy	507	506	− 0.2
Central service	756	869	14.9
X-ray	744	712	− 4.3
DRG 211 Hip/Femur§			
Patients, No.	13	29	123.1
Average length of stay, d	10.6	8.7	−17.9
Average age, yr	54	78	
Average charge per patient, $			
Total gross revenue	12,254	12,275	0.2
Pharmacy	873	857	− 1.8
Surgery	3,001	3,069	2.3
Laboratory	520	924	77.7
Physical therapy	596	462	−22.5
Central service	560	755	34.8
X-ray	535	668	24.9
DRG 212 Hip/Femur‖			
Patients, No.	4	5	25.0
Average length of stay, d	8.5	8	− 5.9
Average age, yr	11	8	
Average charge per patient, $			
Total gross revenue	9,600	10,066	4.9
Pharmacy	597	501	−16.1
Surgery	2,655	3,258	22.7
Laboratory	427	446	4.4
Physical therapy	189	168	−11.1
Central service	360	511	41.9
X-ray	356	567	59.3

*Inlier population is defined as those patients with a length of stay ± 1 standard deviation from the average.

†Charges are adjusted for price increases between 1987 and 1988.

‡Hip and femur procedures except major joint procedures, in patients 18 years and older, with complications or comorbidity

§Hip and femur procedures except major joint procedures, in patients 18 years and older, without complications or comorbidity.

‖Hip and femur procedures except major joint procedures, in patients aged 0 to 17 years.

(Washington Post: "$125 Billion in Waste Alleged in U.S. Hospital, Surgical Costs," *San Francisco Chronicle,* May 4, 1988, p A16). If a total of $600 billion was spent for health care in 1989, this means that more than 20% of the services provided could be considered expendable. Much of this waste has been trimmed through utilization controls, reducing the amount of unnecessary hospital admissions and non-acute-care hospital days, and substituting less costly outpatient services for inpatient care when clinically appropriate.

Other medical studies have shown that many of the services physicians provide may not be clinically appropriate.[6-8] Studies on the appropriateness of coronary angiography, carotid endarterectomy, endoscopy, coronary artery bypass procedures, and cesarean sections suggest that as many as 25% to 75% of these services have been carried out for inappropriate clinical reasons.

With the continued introduction of new, more advanced, and more expensive technology, another peculiarity has occurred in the way resources are used. While these new technologies provide additional information, there is no concomitant reduction in the use of older technologies, so the costs continue to soar. Do oral cholecystograms, ultrasonograms, and computed tomographic scans need to be done on every patient with possible gallbladder disease?[9] There is still much to be learned about the effective use of health care resources.

Results and Discussion

The potential for improving efficiency is there; the question is how to make it work. Can we influence positive change by modifying physician behavior?

Going back to the orthopedic project discussed earlier, we compared the results from the preeducation year 1987 with those from the posteducation year 1988 (Table 6). For the sake of analysis, results are reported by DRG groups for inlier cases only—that is, those patients with lengths of stays ± 1 standard deviation from the average. Most of the results indicate a positive change. Lengths of stay were reduced an average of 14%, pharmacy charges were down 11%, laboratory charges were down 13%, and total average charges per patient were reduced by almost $1,000.

Our results are consistent with the findings of other studies in the literature. Whereas some studies have shown equivocal results, others have documented reductions that average 10% to 20% in total charges, lengths of stay, the number of diagnostic studies, and the use of other ancillary services after the introduction of comprehensive physician educational programs.[10-12] It is certainly worth trying (R. Winslow, "AMA, Rand Go After Modern Ill: Unneeded Procedures," *Wall Street Journal,* March 22, 1990, pp B1,6; K. Glenn, "Rising Health Costs Spur Studies, Guidelines on Use of Procedures," *Physician's Financial News,* August 15, 1989, p 2; R. McGuire, "Practice Guidelines in Development," *Medical Tribune,* July 12, 1990, p 13).

In the final analysis, physicians need to become involved as true resource managers to maintain internal control of the system. A more efficient use of resources will benefit all segments of the medical market. Payers will appreciate the financial equity gained from more cost-effective health care spending. Providers and patients should appreciate improvements in quality through more effective treatment and outcome. Society will gain by having more services available for those in need through a more effective allocation of resources.

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Conferences and Reviews

Retinal Vasculitis—A Primer

JAMES T. ROSENBAUM, MD; JOSEPH E. ROBERTSON, Jr, MD; *and* ROBERT C. WATZKE, MD, *Portland, Oregon*

Retinal vasculitis is a diagnosis that is generally suggested by an ophthalmologist. Frequently patients with the disorder are referred to nonophthalmologists for further diagnostic evaluation or treatment. The criteria for defining vasculitis differ greatly between ophthalmologists and other physicians. To facilitate collaboration between ophthalmologists and their colleagues, we have sought to clarify the term "retinal vasculitis" by discussing its subcategories, the potential role of antiphospholipid antibodies, and the etiology of retinal vasculitis. We offer guidelines for evaluating the disorder and treating patients.

(Rosenbaum JT, Robertson JE Jr, Watzke RC: Retinal vasculitis—A primer. West J Med 1991 Feb; 154:182-185)

Retinal vasculitis is defined clinically as an abnormal appearance of the retinal vasculature due to inflammation. An ophthalmologist diagnoses vasculitis based on a direct visualization of the vessels and rarely has the benefit of pathologic confirmation; in contrast, vasculitis in most locations other than the eye is usually diagnosed and classified on the basis of pathologic findings (Table 1).[1] Thus, subcategories of systemic vasculitis including leukocytoclastic vasculitis, granulomatous angiitis, giant cell arteritis, systemic necrotizing vasculitis, and thromboangiitis obliterans are essentially pathologic diagnoses. In many cases, abnormalities of retinal vessels may be caused by perivascular changes rather than true disease in the vessel wall itself. Furthermore, although microvascular involvement in some organ systems may produce no symptoms, microvascular inflammation in the retina often has major and immediate visual consequences.

Many pathologic processes can affect the retinal vasculature and produce clinical findings similar to retinal vasculitis. A strict definition of retinal vasculitis excludes forms of vasculopathy due to noninflammatory processes such as atherosclerosis, congenital anomalies, or increased blood viscosity (Table 2). Inflammation may involve retinal arteries, veins, or capillaries, although venous involvement is more commonly recognized. Patients with retinal vasculitis may report reduced visual acuity, cloudy vision, diminished color appreciation, a sensation of flashing lights (photopsia), or floaters (Table 3). Some patients with retinal vasculitis are asymptomatic. The disorder by itself should not produce pain or ocular redness. One hallmark of retinal vasculitis (Table 4) is a vascular sheathing (Figure 1), which seems to correlate with a perivascular infiltrate of inflammatory cells seen on pathologic specimens.[2] Sheathing, however, is not specific for vasculitis and frequently appears, such as after a retinal vein occlusion. Inflammation involves noncontiguous portions of the vessel, is often associated with inflammatory cells in the overlying vitreous, and does not initially narrow the vessel. In contrast, sheathing due to atherosclerosis frequently occurs along with vessel narrowing, microvascular anomalies, lipid exudates, and increased light reflexes. Retinal vasculitis can result in various other nonspecific findings including cotton-wool spots or cytoid bodies (Figure 2), which are indicative of retinal ischemia; hemorrhage; Roth's spots (Figure 3), which are hemorrhages with a white center[3]; and the abrupt occlusion of retinal vessels, macular edema, or optic disc edema. Abnormal attenuation of vessels may appear as an end stage of vasculitis. Additional evidence of ocular inflammation, such as leukocytes in the vitreous humor, frequently accompanies retinal vasculitis.

Retinal vessels can be visualized directly with instruments such as a hand-held direct ophthalmoscope, an indirect ophthalmoscope, or the combination of a slit-lamp biomicroscope with an appropriate contact lens. Close scrutiny under high magnification is often required to detect vascular change. Small patches of vasculitis or peripheral retinal involvement are difficult to see by direct ophthalmoscopy. The retinal vessels are also evaluated by fluorescein angiography. The intravenous administration of sodium fluorescein permits excellent definition of the retinal vasculature. These vessels do not normally permit the extravasation of this dye. Fluorescein staining of the vessel wall does occur if the vessel is inflamed.

Retinal vasculopathy can be divided into subcategories (Table 2). Atherosclerosis, including that associated with diabetes mellitus, is the most common cause of abnormal retinal vessels but is not primarily an inflammation. Abnormal retinal vessels can result from congenital anomalies as in Coats' disease. Abnormal blood viscosity from hemoglobinopathies, leukemia, or paraproteinemias also produces abnormal retinal vessels.

Inflammatory conditions involving retinal vessels can also be subdivided. First, certain systemic illnesses (Table 5) such as Behçet's disease or sarcoidosis (Figures 4 and 5) may be associated with retinal vasculitis. Although sarcoidosis is not regarded as a systemic vasculitis, its ability to involve the wall of the retinal vasculature has been confirmed histologically.[4] Most forms of systemic vasculitis such as polyarteritis nodosa,[5] Churg-Strauss vasculitis,[6] or Wegener's granulomatosis[7] can involve retinal vessels. These are rare diseases, however, that only infrequently manifest as a retinal vasculitis. Temporal arteritis is well known for its ability to cause retinal ischemia through involvement of the ophthalmic or

From the Division of Arthritis and Rheumatic Diseases, Departments of Medicine (Dr Rosenbaum), Ophthalmology (Drs Rosenbaum, Robertson, and Watzke), and Cell Biology (Dr Rosenbaum), Oregon Health Sciences University School of Medicine, Portland.

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Reprint requests to James T. Rosenbaum, MD, Oregon Health Sciences University, L329A, 3181 SW Sam Jackson Park Rd, Portland, OR 97201.

central retinal artery, but involvement of branch retinal arteries or veins has not to our knowledge been described. Multiple sclerosis[8] and Crohn's disease[9] have also been reported in association with retinal vasculitis. Systemic lupus erythematosus frequently produces retinal ischemia as manifested by cotton-wool spots,[10] but these are usually asymptomatic. Visually significant retinal vasculitis in association with systemic lupus is well described but uncommon.[11]

TABLE 1.—*Differences Between Retinal and Systemic Vasculitis*

Basis for Diagnosis	*Vasculitis*	
	Retinal	*Systemic*
Size of vessel involvement	Microvascular to small	Variable, but microvascular involvement not clinically important
Histologic findings	No	Yes

TABLE 2.—*Classification of Retinal Vasculopathy*

Disease	*Example*
Noninflammatory	
Atherosclerosis	Diabetes mellitus
Congenital anomalies	Coats' disease
Increased blood viscosity	Hemoglobinopathies, paraproteinemias
Inflammatory	
Secondary to chorioretinal inflammation	Toxoplasmosis, cytomegalovirus
As part of systemic disease	Sarcoidosis, Behçet's syndrome, polyarteritis
Vaso-occlusive disease	Anticardiolipin antibody-mediated
Primary retinal vasculitis	Eales disease, frosted branch angiitis

TABLE 3.—*Symptoms Associated With Retinal Vasculitis*

Reduced visual acuity	Central scotoma
Cloudy vision	Unusual numbers of floaters
Photopsia	Reduced color appreciation

TABLE 4.—*Physical Findings Associated With Retinal Vasculitis*

Vascular sheathing	Roth's spots
Attenuated vessels	Optic disc edema
Occluded vessels	Macular edema
Cytoid bodies	Optic nerve pallor
Cotton-wool spots	

TABLE 5.—*Systemic Illnesses Associated With Retinal Vasculitis**

Sarcoidosis	Churg-Strauss vasculitis
Behçet's disease	Antiphospholipid antibody syndrome
Systemic lupus erythematosus	Tuberculosis
Syphilis	Subacute bacterial endocarditis
Crohn's disease	Primary Sjögren's syndrome
Polyarteritis nodosa	Multiple sclerosis
Wegener's granulomatosis	Whipple's disease
Relapsing polychondritis	Malaria

*Excludes illnesses associated with vasculopathy rather than vasculitis.

A second subcategory of retinal vasculitis occurs in a localized area of chorioretinal inflammation. For example, in toxoplasmosis, acute retinal necrosis, or retinitis due to cytomegaloviral infection (Figure 6), retinal vessels adjacent to the area of chorioretinitis are frequently abnormal. The characteristics of the accompanying chorioretinal lesion should help direct the diagnostic evaluation of these diseases.

A third form of vascular abnormality appears primarily as vaso-occlusive disease. Antiphospholipid antibodies such as the lupus anticoagulant or anticardiolipin antibodies have definitely been associated with vaso-occlusive disease.[12] Increasing evidence suggests that these antibodies can be associated with retinal occlusive disease in patients with systemic lupus erythematosus[13] and in others who do not meet diagnostic criteria for lupus.[14,15] A search for these antibodies should be made in any patient who has evidence of an occlusive form of retinal vasculopathy. Patients with lupus who have retinal vascular disease secondary to anticardiolipin antibodies are more likely to have central nervous system disease. A rare microangiopathic syndrome resulting in the occlusion of retinal and cerebral vessels has been described.[16,17] The role of antiphospholipid antibodies in this condition is unknown.

Finally, many patients fall outside all of these disease subcategories and suffer from an idiopathic syndrome that has no apparent systemic correlate (Figures 7 and 8). We suggest that this disorder be labeled primary retinal vasculitis to indicate its distinctness from the subcategories we have discussed. Examples of primary retinal vasculitis include Eales disease[18] and frosted branch angiitis.[19] Eales disease refers to a periphlebitis that involves primarily vessels in the periphery of the retina (Figure 1).

In theory, the distinction between inflammatory and noninflammatory forms of vasculopathy should be clear-cut. Nonetheless, regardless of its cause, ischemia can produce secondary inflammatory changes.[20] Vascular changes due to emboli can easily be confused with an inflammatory event originating in the vessel wall. Further, occlusive disease frequently coexists with other vascular abnormalities. Systemic lupus erythematosus is a classic example of an illness that produces both occlusive vascular changes and vascular sheathing, as seen in a primary vasculitis.

Etiologic Considerations

With rare exceptions, such as toxoplasmosis or antiphospholipid antibody-mediated disease, the cause of retinal vasculitis is unknown. Tuberculosis, an extremely rare cause of uveitis in this country, was once presumed to be a common cause of retinal vasculitis. A delayed hypersensitivity response to purified protein derivative has been reported in nearly 50% of patients with Eales disease.[18] The role of this immune response in the pathogenesis of the vasculitis is not clear at this time. Antituberculous therapy has not been useful in patients with Eales disease or forms of retinal vasculitis unaccompanied by tuberculous uveitis.

Retinal vasculitis can be produced experimentally in animals by provoking an immune response against rhodopsin kinase, also known as retinal S antigen.[21] A chorioretinitis occurs along with the retinal vessel involvement. Increasing evidence supports the concept that the microvascular endothelium is intrinsically different from large-vessel endothelium.[22] It may be that unique antigens expressed by retinal vascular endothelial cells expose the vessel to immune-medi-

ated damage. Alternatively, retinal vessels may be unique in their response to specific immune complexes.

Laboratory Evaluation

The laboratory evaluation of cases of retinal vasculitis is determined largely by the results of a patient's history and physical examination. If present, a systemic illness such as Behçet's disease, polyarteritis nodosa, or systemic lupus erythematosus should be suggested by a thorough medical history. Despite the potential for a systemic process to involve retinal vessels, most patients with retinal vasculitis have no evidence of a disease process outside the eye. A recently

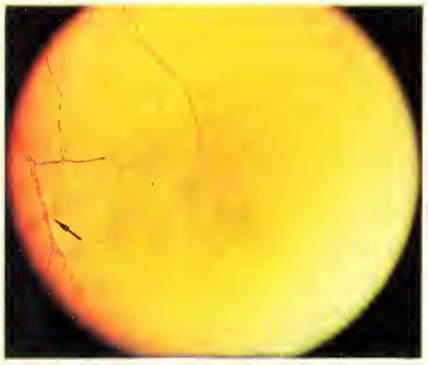

Figure 1.—The photograph shows a peripheral retinal vessel of a patient with idiopathic retinal vasculitis (Eales disease). The arrow indicates an area with significant vascular sheathing.

Figure 2.—A cotton-wool spot **(arrow)** indicates that local retinal ischemia is present just temporal to the optic nerve.

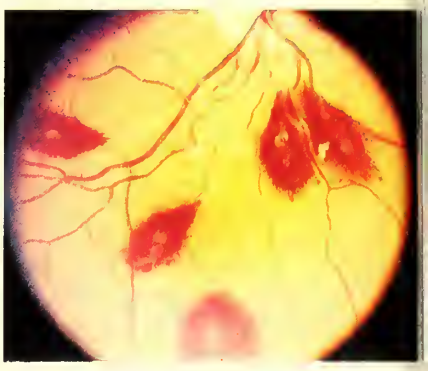

Figure 3.—Multiple Roth's spots on the fundus of a patient with acute leukemia are evident as hemorrhages with a white center.

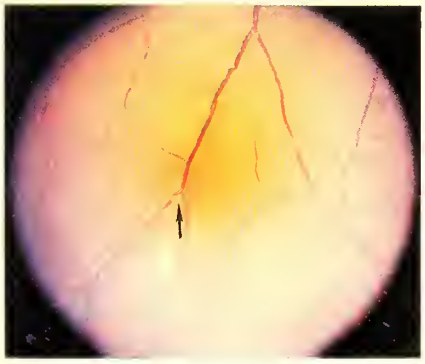

Figure 4.—The fundus photograph shows the peripheral retinal vessels of a patient with known sarcoidosis. The whitish perivascular infiltrates **(arrow)** are called candle-wax dripping.

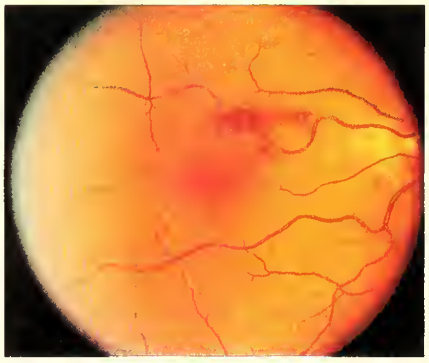

Figure 5.—In this fundus photograph of a patient with sarcoidosis, there is an area of hemorrhage and interruption of vascular flow.

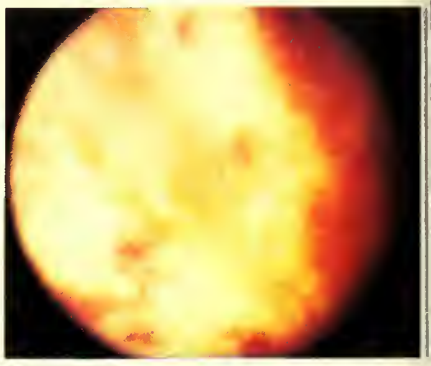

Figure 6.—The fundus of a patient with the acquired immunodeficiency syndrome and cytomegalovirus retinitis is shown. In association with the whitish areas of confluent retinitis, the retinal vessels are clearly abnormal with areas of attenuation, tortuosity, and hemorrhage.

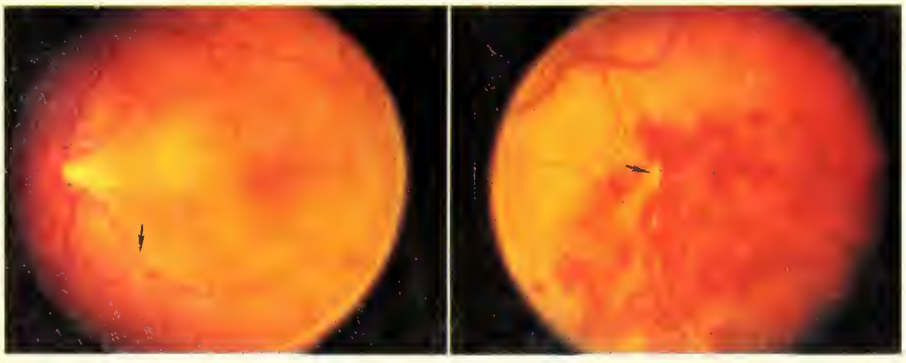

Figure 7.—**Left,** The fundus of the left eye of a patient with a primary retinal vasculitis shows abnormal vessels in the posterior pole. Note particularly the irregularity of the artery for the inferior temporal arcade **(arrow)**. The haze or reduced clarity of the photograph is due to associated inflammation in the vitreous. **Right,** In another photograph of the same eye, the vessel in the periphery **(arrow)** is occluded with surrounding hemorrhage.

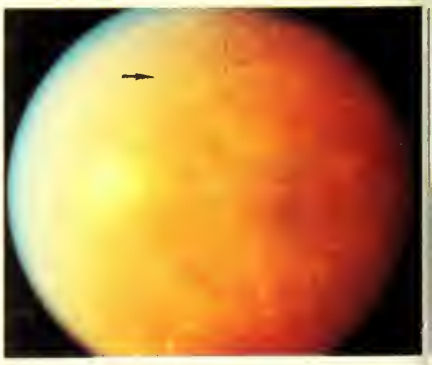

Figure 8.—The photograph shows the posterior pole of the same eye depicted in Figure 7 taken 2½ years later. Despite aggressive therapy including oral corticosteroids, periocular corticosteroids, azathioprine, intravenous cyclophosphamide, and cyclosporine at various times, the eye disease has progressed. The inferior temporal artery is now occluded, and the superior temporal artery has obvious sheathing **(arrow)**. The disc shows marked pallor.

reported southern California survey of patients with uveitis included 41 with retinal vasculitis.[23] In 38 of these patients, no underlying illness was found. In the remaining 3 patients, the vasculitis was presumed to be secondary to a systemic viral illness. In contrast, a recent British study found that many patients with retinal vasculitis do have a systemic illness, usually Behçet's disease or sarcoidosis.[24] Our own clinical experience concurs with the California report in that Behçet's disease is rare in our patient population. It accounts for about 0.4% of patients with intraocular inflammation in our demographic group. If a chorioretinal lesion accompanies the vasculitis (secondary retinal vasculitis), a specific disorder, such as toxoplasmosis, acute retinal necrosis, or cytomegaloviral infection, may be suggested. Occlusive lesions should prompt a search for antiphospholipid antibodies, and emboli arising from the heart or great vessels should be excluded.

Without signs or symptoms pointing to a specific illness, we frequently obtain a complete blood count; a chemistry screen that includes liver and renal function studies, the quantitation of serum globulin levels, and serum glucose values; a urinalysis to exclude glomerular involvement; and a sedimentation rate. These tests are rarely useful in arriving at a specific diagnosis, but they are relatively inexpensive and generally provide baseline values that could be affected by several therapeutic choices.

A chest roentgenogram is a more critical study. The chest film may show adenopathy suggestive of sarcoidosis, a disease often initially symptomatic in the eye.[25] In addition, we prefer the chest x-ray study over a purified protein-derivative skin test as a screening device for tuberculosis because skin tests are frequently positive in patients with retinal vasculitis but have no therapeutic implication. Finally, syphilis can present as a retinal vasculitis[26] and should be excluded by a serologic study such as a fluorescent treponemal antibody absorption test. Many patients with retinal vasculitis that seems confined to the eye have systemic immunologic abnormalities such as detectable circulating immune complexes.[27,28] An association with HLA-DR4 has also been reported.[29] We do not routinely search for these abnormalities because present knowledge does not assign them therapeutic or prognostic importance. Similarly, a test that is positive for antinuclear antibodies does not establish a diagnosis of systemic lupus erythematosus.[30] This test is therefore done only if other aspects of the presentation suggest this diagnosis.

Treatment

The treatment of retinal vasculitis depends on the detection of an associated condition, the severity of the disease, and whether the process is unilateral or bilateral. If its cause is infectious, the disorder should be managed with appropriate antibiotic therapy. In the absence of a specific infection, the periocular administration of corticosteroids may help control the inflammation. We elect not to institute any therapy for many patients with retinal vasculitis. For example, patients with Eales disease often have a smoldering course, and the peripheral nature of the disease spares central acuity. Because present therapy is palliative rather than curative, patients may need to accept some degree of visual loss rather than undergo potentially toxic therapy. If the disease is bilateral and interferes considerably with activities of daily living, parenteral corticosteroid therapy at an initial dose equivalent of 40 to 60 mg of prednisone per day is sometimes effective. No controlled studies have been done on the treatment of retinal vasculitis. We reserve systemic immunomodulatory therapy beyond corticosteroids for those patients with active inflammation, bilateral inflammation, and a best-corrected vision of no better than 20/50. The use of cyclosporine has been beneficial in a limited number of patients.[31] We have used azathioprine or cyclophosphamide at dosages comparable to what has been suggested for patients with systemic vasculitides.[1] Many authorities recommend anticoagulation for vascular disease due to antiphospholipid antibodies.[15] The prognosis for retinal vasculitis is variable, reflecting the heterogeneous nature of this group of disorders.

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Conferences and Reviews

Brain Tumors

Moderator
KEITH L. BLACK, MD

Discussants
JOHN C. MAZZIOTTA, MD, PhD, *and* DONALD P. BECKER, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the University of California, Los Angeles, School of Medicine. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

Recent advances in experimental tumor biology are being applied to critical clinical problems of primary brain tumors. The expression of peripheral benzodiazepine receptors, which are sparse in normal brain, is increased as much as 20-fold in brain tumors. Experimental studies show promise in using labeled ligands to these receptors to identify the outer margins of malignant brain tumors. Whereas positron emission tomography has improved the dynamic understanding of tumors, the labeled selective tumor receptors with positron emitters will enhance the ability to specifically diagnose and greatly aid in the pretreatment planning for tumors. Modulation of these receptors will also affect tumor growth and metabolism. Novel methods to deliver antitumor agents to the brain and new approaches using biologic response modifiers also hold promise to further improve the management of brain tumors.

(Black KL, Mazziotta JC, Becker DP: Brain tumors. West J Med 1991 Feb; 154:186-197)

Peripheral Benzodiazepine Receptors—Mechanisms in Brain Tumor Biology

KEITH L. BLACK, MD*: There are two classes of benzodiazepine receptors in mammalian tissues. One class of receptors (the "central" receptor) is located on neurons and is the site at which benzodiazepine ligands are thought to exert their antianxiety, anticonvulsant, and muscle relaxant effects.[1-3] These central binding sites are closely linked to γ-aminobutyric acid (GABA) receptors, modulate the GABA-regulated anion channel, and are located on the cell membrane.[2,4,5] The second class of benzodiazepine receptors (the "peripheral," nonneural receptor) is sparse in normal nervous tissue but prominent in many other tissues, such as kidney, heart, platelets, and lymphocytes.[6-8] High-affinity binding by peripheral benzodiazepine ligands to rodent glial tumor was shown in homogenate studies.[8-12] Based on these findings, it was recently suggested that peripheral benzodiazepine receptor ligands could be used specifically to image glial tumors in vivo and provide better definition of tumor borders and biologic character.[13,14] Second, but no less important, the dramatic increase in the expression of peripheral benzodiazepine receptors in brain tumors has recently prompted further investigation into a possible role of these receptors in brain tumor biology. Because the receptor was shown to localize on the outer membrane of mitochondria, considerable work has focused on the modulation of cell metabolism by the peripheral benzodiazepine receptor. Recent work has also suggested that selective peripheral benzodiazepine ligands may act as mitogenic agents and increase tumor cell proliferation and DNA synthesis.

Brain Tumor Imaging

Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) techniques currently used to image tumors in the central nervous system rely on differences in tissue attenuation characteristics, a breakdown of the blood-brain barrier to contrast agents, mass effect, or changes in glucose or amino acid transport.[15] The limitations of these methods, most apparent in glial and other infiltrative tumors, are due to their failure to identify tumor cells that reside beyond the borders of the imaging abnormality.[16] An ability to image tumors with a ligand that binds specifically to tumor cells and readily crosses the intact blood-brain barrier might significantly improve tumor resolution in the brain and permit better identification of the outermost margin of tumor cells. Peripheral benzodiazepine receptor ligands seem to fulfill both criteria: they are not barred by the blood-brain barrier, and they have high specific binding to glial tumors.

The possibility that a peripheral benzodiazepine receptor ligand might be used specifically to image glial tumors was first suggested by the findings of Starosta-Rubinstein and associates.[13] Published findings from our laboratory were in agreement with this previous report that peripheral benzodiazepine ligands bind selectively to glial tumors in rats, with little binding to normal brain or necrotic tissue.[14] The intravenous administration of the selective peripheral benzodiazepine ligand, [^{3}H]PK 11195 (1-[2-chlorophenyl]-*N*-methyl-*N*-[1-methylpropyl]-3-isoquinoline carboxamide),

*Assistant Professor, Department of Surgery, Division of Neurosurgery, UCLA School of Medicine.

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Reprint requests to Keith L. Black, MD, Division of Neurosurgery, 74-140 Center for the Health Sciences, 10833 Le Conte Ave, UCLA School of Medicine, Los Angeles, CA 90024-1749.

ABBREVIATIONS USED IN TEXT

CT = computed tomography
ED_{50} = median effective dose
MRI = magnetic resonance imaging
PET = positron emission tomography

or the mixed peripheral and central ligand, [^{3}H]flunitrazepam (after pretreatment with clonazepam to block central binding sites), showed binding densities of peripheral benzodiazepine receptors threefold to fivefold higher in experimental glial tumors compared with normal cortex. Peripheral binding could be displaced by the preadministration of excess PK 11195. Topographic correlation was excellent between areas of histologically verified tumor and high densities of peripheral benzodiazepine binding (Figure 1). It was further shown, however, that peripheral benzodiazepine binding was not exclusive to tumors of glial origin but that, in fact, substantial binding occurred in the experimental metastatic tumors. The nonexclusive binding of peripheral benzodiazepines to glial tumors was further supported by in vitro findings that peripheral ligands will bind to various tumors in humans (Table 1),[17] which suggests that they may have limited use as a marker to differentiate tumors. We did, however, find a significant correlation between high binding and the degree of malignancy in gliomas in humans (Table 2). In vitro studies also showed that the number of receptors (B_{max}) on C6 and Walker 256 tumors was increased rather than the affinity of the ligand for the receptor site (Table 3).[18]

Three-dimensional reconstructions were recently applied to autoradiographic images of peripheral benzodiazepine binding and compared with histologic images to confirm the spatial and structural accuracy of receptor mapping images in an experimental glial tumor. A close topographic correlation between histologic features and tumor binding was found. Similar techniques using positron-labeled peripheral benzodiazepine receptor ligands are now being applied in humans. Although current PET resolution is limited, small clusters of tumor cells may be located using these techniques. This could have important implications in identifying the surgical margins in subgroups of patients without diffuse spread of glial tumor cells where radical resections may prove beneficial. Based on the intensity of uptake, insight may be obtained into the biologic behavior of the tumor to help in preoperative planning and in determining prognosis.

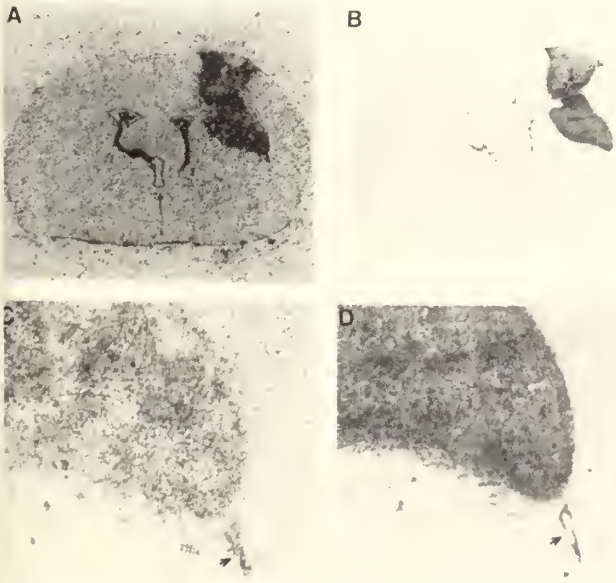

Figure 1.—A digitized autoradiogram **(A)** and thionin-stained section **(B)** show RG-2 tumor after the administration of [^{3}H]flunitrazepam with clonazepam. Binding to normal brain is slightly higher compared with [^{3}H]PK 11195 administration. In magnified comparisons of the same autoradiogram **(C)** and thionin-stained section **(D)**, tumor definition and correlation with histologic features remain high. A fingerlike projection of invading cells **(arrow)** seen on the magnified thionin-stained section **(D)** is also visualized on the magnified autoradiogram **(C; arrow)**.

Tumor Biology

The biologic role of peripheral benzodiazepine receptors in brain tumors is unclear. Unlike the central receptor, which is located on the cell membrane, the peripheral binding site is localized to the mitochondrial and nuclear subcellular fractions,[19,20] which implies a role for the receptor in oxidative metabolism and ion fluxes.

Studies of the effects of peripheral-type ligands have also reported an inhibition of the proliferation of thymoma cells,[21] the suppression of thymidine incorporation into the DNA of glial cells,[22] the blocking of mitogenesis in Swiss 3T3 cells, and the induction of differentiation in Friend erythroleuke-

TABLE 1.—*Specific Binding of [^{3}H]PK 11195 to Nongliol Humon Broin Tumors**

Histologic Tumor Type	*Specific Binding, fmol/mg tissue*
Sarcoma	510.0
Meningioma	353.7 ± 93.6
Hemangiopericytoma	180.9
Primitive neuroectodermal tumor, n = 2	154.3
Craniopharyngioma	107.7
Normal	77.7 ± 28.4

*Values are expressed as the mean when n = 1. Standard deviation values are given when n ≥ 2.

TABLE 2.—*Specific Binding of [^{3}H]PK 11195 to Gliol Tumors in Humans**

Histologic Tumor Type	*Specific Binding, fmol/mg tissue*
Normal, nonneoplastic	77.7 ± 28.4
Necrosis	74.8 ± 38.0
Infiltrated	219.8 ± 31.9
Low-grade glioma	267.3 ± 54.0
High-grade glioma	452.1 ± 46.5

*For statistical analysis (analysis of variance and unpaired Student's *t* test), regions of interest were defined as nonneoplastic (no neoplastic cells), necrotic (nonviable debris), infiltrated (tumor cells mixed with histologically appearing normal cells), low grade (glioma grades I and II), and high grade (glioma grades III and IV). The 3 necrotic sections were all from patients with high-grade gliomas. Infiltrated sections included patients from the high- and low-grade groups. Significant differences were found between nonneoplastic versus infiltrated ($P < .0005$), nonneoplastic versus low-grade ($P < .0005$), nonneoplastic versus high-grade ($P < .0005$), infiltrated versus high-grade ($P < .0005$), and low-grade versus high-grade ($P < .005$) tumors.

TABLE 3.—*Specific Binding of [^{3}H]PK 11195 to Rot Tumors**

Tissues	*K_d, nmol/liter*	*B_{max}, fmol/mg*
C6 glioma	2.09±0.74	1,089.3±232.2
RG-2 gliomas	2.29±0.30	1,027.3± 78.7
Walker	2.17±0.24	924.2±183.7
Normal cortex	2.04±0.49	62.1± 12.8

*Dissociation constant (K_d) and maximum benzodiazepine receptor (B_{max}) values for [^{3}H]PK 11195 in experimental tumors and normal rat brains are determined by Scatchard analysis. Values are expressed as the mean ± standard deviation of 3 independent experiments.

mia cells.[23] On the other hand, they enhance melanogenesis in melanoma cells[24] and enhance the specific induction of c-*fos* messenger RNA and protein by nerve growth factor more than 100-fold.[25] Diwan and co-workers reported the promotion of hepatocellular carcinogenesis in B6C3F1 mice by diazepam after initiation by *N*-nitrosodiethylamine.[26] These effects, however, were found at micromolar concentrations, whereas peripheral benzodiazepine receptors were saturated at concentrations in the nanomolar range.[9,21,27]

Because of the discrepancy between the dose of peripheral benzodiazepines needed to show growth control and their binding constants, we recently investigated the effects of peripheral benzodiazepines on cell proliferation of C6 glioma and on the mitogenesis of Swiss 3T3 cells in culture within the concentrations at which receptor binding occurs.[28] We found that PK 11195 increased the growth rate of C6 glioma cells by 20% to 30% in the nanomolar range in serum-free medium. Incorporating tritium-labeled thymidine into C6 glioma cells also increased their growth rate 22% and 25%, respectively, after treatment by the selective peripheral benzodiazepine ligands, PK 11195 and Ro 5-4864. When the effect of PK 11195 as a mitogenic agent was estimated by [^{3}H]thymidine incorporation using Swiss 3T3 cells, PK 11195 was found to increase DNA synthesis 170% over that of control at 10 nmol per liter. Higher concentrations of benzodiazepines inhibited DNA synthesis. Peripheral benzodiazepine binding sites, however, were shown to decrease in number after exposure to serum-free medium or to 10 nmol per liter of PK 11195.

It seems that peripheral benzodiazepine ligands have biphasic effects on cell proliferation. At concentrations in the nanomolar range, they stimulate [^{3}H]thymidine incorporation into DNA and increase cell proliferation in C6 glioma. They also show mitogenic activity in cell lines such as Swiss 3T3 cells. At micromolar concentrations, however, they inhibited DNA synthesis. Other authors, who have also suggested that peripheral benzodiazepines are involved in regulating cell proliferation,[21-25] have indicated an antiproliferative effect of benzodiazepines at the micromolar range. Pawlikowski and colleagues reported an antiproliferative action of peripheral-type benzodiazepines on human glioma at the micromolar range (1 to 100 μmol per liter).[22] A strong positive correlation between the binding affinity of benzodiazepines for the peripheral-type receptor and their antiproliferative activities was reported in mouse thymoma cells,[21] though there was no significant correlation between the activities of benzodiazepines and their reported degree of affinity.[6,23,24,29] In Wang's experiments there was an approximately 2,000-fold difference in dosage between receptor binding and biologic effects[21]; the median effective dose (ED_{50}) for Ro 5-4864 in inhibiting [^{3}H]thymidine incorporation into thymoma cells was 16.1 μmol per liter, whereas the intensity concentration where 50% of receptors were bound (IC_{50}) was 8.5 nmol per liter. An in vitro binding assay using autoradiography or cell homogenates showed that peripheral benzodiazepine binding should be saturated at 10 to 20 nmol per liter.[18,21] Clarke and Ryan used erythroleukemia cells in their study and concluded that differentiation was induced by the lipophilic properties of certain benzodiazepines.[23] To the contrary, the stimulation of cell growth of C6 cells and mitogenic activity of Swiss 3T3 cells were found in the nanomolar range, which corresponded to the binding affinities of the compounds for the peripheral benzodiazepine receptors. Ruff and associates also reported that the chemotaxis of human monocytes was enhanced with an ED_{50} of 10^{-13} mol per liter for Ro 5-4864, whereas a higher concentration ($>10^{-8}$ mol per liter) resulted in a reduced chemotactic response.[30] These findings also support our conclusion that peripheral benzodiazepines have a biphasic effect on cell proliferation.

Peripheral benzodiazepines, however, are not polypeptide growth factors like epidermal growth factor or platelet-derived growth factor that has been found to be active on glial cells. Also, because receptors for peripheral benzodiazepines are thought to localize on the mitochondrial outer membrane,[19,20] it will be worthwhile to investigate in future studies whether this receptor-ligand complex will significantly affect the mitochondrial DNA or whether the activated receptor transmits mitogenic signals to the nucleus.

Clinical Implications

Selective high-density binding by peripheral benzodiazepine ligands could be used clinically in several ways. First, these ligands are amenable to conjugation with potentially cytotoxic compounds. The localization of binding sites to nuclear and mitochondrial fractions could increase their therapeutic advantage compared with targets on the cell surface. The effect of the modulation of the peripheral receptor itself on tumor growth and differentiation also remains to be explored. Further, positron-labeled benzodiazepine ligands, such as carbon 11-labeled PK 11195, could potentially improve the definition of the outer border of tissues infiltrated with malignant tumor cells or indicate residual tumor after surgical therapy. These novel concepts are currently being investigated.

Positron Emission Tomography in the Study of Cerebral Neoplasms

Approaches to Brain Tumor Imaging

JOHN C. MAZZIOTTA MD, PhD*: Although anatomically based imaging techniques have provided substantial information about cerebral gliomas, they can be inconclusive in detecting early tumors, in discriminating tumors from edema, the histologic grading of tumors, and in differentiating tumor recurrence from radiation necrosis.[31] Structural imaging techniques, such as x-ray computed tomography and magnetic resonance imaging, provide high-quality, high-resolution images of the site of cerebral neoplasms and the distortions they induce in adjacent cerebral structures by the mass effects caused by their own volume and attendant edema. In addition, by using agents such as iodinated contrast material in x-ray CT, alterations in the blood-brain barrier may also be detected by these techniques. Distinguishing actual sites of viable tumor from zones of necrosis or surrounding edema is difficult with such methods, however. Similarly difficult is clinically differentiating recurrent tumor from radiation necrosis in a patient who has new signs and symptoms that are referable to a site of previous tumor therapy.

Positron emission tomography measures a wide range of physiologic processes critical in understanding the pathophysiology of cerebral disorders.[32-35] These processes include the ability to examine cerebral physiology, biochemistry, hemodynamics, and pharmacokinetics in vivo in health and disease. Critical to the understanding of tumor growth and strategies to limit or block such growth is a knowledge of

*Associate Professor, Department of Neurology/Radiological Sciences, Reed Neurological Institute, UCLA School of Medicine, Laboratory of Nuclear Medicine.

tumor metabolism, blood flow, protein synthesis, blood-brain barrier integrity, and the binding of specific compounds to receptors found on tumor cell surfaces. Each of these processes is important, but the study of the biochemical relations between the processes—that is, stoichiometry—may provide an even more sensitive indicator of tumor type, grade, and natural history.[4] In addition, the effect of the tumor on adjacent or distant tissue is important in understanding the constellation of signs and symptoms manifested by a patient at a given point in time. Thus, tumor edema may produce dysfunction in adjacent tissue either directly or by secondary ischemia. Simultaneously, functional deafferentation and deafferentation of pathways leading to and from the zone of tumor and edema may disrupt normal neuronal activity at far distant sites within and between the cerebral hemispheres and that affecting cerebrocerebellar neuronal connections.[34] Positron emission tomography can identify such local and distant functional disconnections.[34]

Because PET provides functional measures of neuronal activity and biochemistry, we can map normal sites of cerebral activity during behavior. Thus, patterns of cerebral metabolism and blood flow change when a subject is asked to do tasks that involve reading, listening, perceiving sensory stimuli, and movement.[32] By having patients with brain tumors perform such tasks, it is possible to identify whether critical neuronal networks, presumed to lie close to the site of a planned tumor resection, will be adversely affected by the surgical procedure, resulting in a major neurologic deficit for the patient.

Positron Emission Tomography

Positron emission tomography is an imaging technique that provides an accurate measurement of the concentrations of trace amounts of compounds labeled with positron-emitting isotopes introduced into the body either by inhalation or intravenous administration.[32] The imaging device produces cross-sectional and planar images of the distribution of the administered radiopharmaceutical agent. With the use of labeled compounds to trace physiologic processes, it is possible to use the local tissue concentrations, obtained from the PET images, to quantify these physiologic processes if the mathematic relation between the process and the concentration of the tracer in the tissue is understood. These mathematic relations are termed tracer kinetic models, and they are needed to understand the behavior of compounds in the body and to interpret the resultant data validly. This usually requires both a measurement of the time course of the concentration of the administered tracer in the blood and sequential images of the organ of interest using PET to determine the tissue tracer concentration. Once the model is validated, the procedure can be simplified and a single set of images can be taken at the end of a defined interval between administering the tracer and acquiring data.

Isotopes that emit positrons have several important qualities. Such isotopes include those of the natural elements of the body, such as nitrogen 13 (^{13}N; 10-minute half-life), carbon 11 (^{11}C; 20-minute half-life), and oxygen 15 (^{15}O; 2-minute half-life). Because these are isotopes of natural biologic elements, they can be incorporated into compounds that faithfully mimic the chemical behavior of the natural compound, thereby minimizing the perturbation of the biologic systems they are intended to trace. Because of the isotopes' short half-lifes, radiation doses to patients are low. A short half-life, however, produces several practical challenges. First, the radiochemical synthesis of the tracer compound must be rapid for there to be enough isotope left at the end of the synthesis for reasonable imaging in a patient. Second, the short half-life of a compound dictates that the isotopes and compounds, in general, must be made at the site of the PET imaging instrument.

TABLE 4.—*Positron Emission Tomography and the Management of Cerebral Gliomas*

Determines tumor grade, which aids in management decisions and guides prognosis
Determines effect of tumor on adjacent and remote cerebral tissues
Monitors progression, change in grade, and therapy effects
Helps in choice of optimal site for biopsy
Differentiates radiation necrosis from tumor recurrence

Isotopes used in PET studies are produced in charged-particle accelerators that include linear accelerators and cyclotrons. At present, the usual approach is to build compact cyclotrons that are used for medical applications, such as the production of positron-emitting isotopes. More than 500 compounds have been labeled with ^{15}O, ^{13}N, ^{11}C, and fluorine 18 (^{18}F) for use with PET.[35,36] These compounds range from simple labeled molecules such as water, carbon monoxide, and oxygen gas to carbohydrates, amino acids, fatty acids, neurotransmitter analogues and precursors, as well as receptor ligands.[35,36]

Positrons are emitted from unstable nuclei and travel a short distance in tissue before coming to rest. Once at rest they combine with nearby electrons, resulting in their mutual annihilation. The resultant energy of annihilation results in two photons emitted at an angle of 180 degrees to one another. These annihilation photons are detected by crystals in the PET camera and are converted into voltages by the system's electronics. Because of the 180-degree emission produced by positron annihilation, crystals on opposite sides of the patient are electronically linked (electronically collimated) to identify those events that take place in a given tomographic plane. This feature permits PET cameras to have uniform, high spatial resolution (state-of-the-art cameras have 6- to 7-mm resolution in all three dimensions).[37]

Thus, with the unique features of PET, including the use of isotopes of natural elements, valid tracer kinetic models, and the unique physical properties of positron decay, it is possible to quantify a wide range of physiologic, biochemical, and hemodynamic processes in the human body using this technique. When applied to the study of cerebral neoplasms, we can use these methods to measure tumor metabolism, blood flow, protein synthesis, blood-brain-barrier integrity, and the binding of specific ligands to membrane receptors. With this unique technique, we can collect previously unavailable data about cerebral neoplasms, which has proved useful in the management of patients with these disorders and in providing insights into the pathophysiology of the neoplastic process itself (Table 4). As these tumor properties are explored with PET, considerable studies have been done and several reviews have been reported.[38-49]

Glucose Metabolism

Tumors have an accelerated rate of glycolysis that can exist despite adequate oxygenation.[50-52] This property, once thought to be unique to tumors, is characteristic of increases

in intermediary metabolism seen with rapidly growing tissue of any type. Weber has shown a correspondence between the rate of tumor metabolism and the growth rate of individual malignant cells[51]; he has attributed this altered metabolism to changes in the concentrations of certain key rate-controlling enzymes in the metabolic pathway. The accelerated glycolytic pathway can be shown with PET studies of glucose metabolism using ^{18}F-labeled fluorodeoxyglucose.[53-55]

In studies of experimentally induced gliomas in animals[56] and human PET studies,[41,57-59] there was evidence of high glucose metabolism within the tumor itself. Hossmann and associates injected intracerebral glioma cells into rats to show that with tumor development, glucose use increased out of proportion to cerebral blood flow.[56] In addition, they found that blood flow decreases in the tissue immediately surrounding the tumor but not in the contralateral hemisphere.

Studies by Di Chiro and colleagues at the National Institutes of Health have shown a remarkable correlation between the metabolic rate and histologic grade of gliomas.[41,57-65] The most consistent finding is the appearance of "hot spots" of hypermetabolism in virtually all grade III and IV gliomas (Figure 2).[41,57-59] Areas of hypermetabolism were only rarely seen in low-grade (I and II) tumors. On average, grade I and II gliomas had metabolic rates similar to that of normal white matter, whereas grade III and IV tumors have metabolic rates comparable with or in excess of normal grey matter (Figure 2).[41] In all cases, peak values for tumor metabolism were used. Similar results were obtained for the gliomas of the upper cervical spinal cord and brain stem.[59,65]

In a separate study by Tyler and co-workers, fluorodeoxyglucose and PET were used to determine tumor glucose metabolism versus tumor grade in 16 patients.[66] Although the highest metabolic rates found were among those patients with grade IV tumors, there were examples of high-grade tumors that apparently had low metabolic rates; all these patients were untreated at the time of tumor metabolism measurements. Tyler and associates analyzed their data in comparison to grey matter of the contralateral hemisphere,[66] whereas the group at the National Institutes of Health used white matter as their reference tissue.[41,58] Thus, there seem to be differences in the interpretation of results, owing in part to the fact that the latter study did not rely on visual inspection of "hot spots" but rather averaged the entire tumor volume and, in addition, studied patients who had been untreated at the time of imaging. Although there is not complete agreement, there generally seems to be an excellent correspondence between the metabolic rate and tumor grade.

The metabolic grading of glioma malignancy has prognostic importance.[67,68] In a study of 45 consecutive patients with proven high-grade gliomas (grades III and IV) studied at the National Institutes of Health, glucose metabolism was evaluated as a measure of prognosis.[67] All patients received radiation therapy before their entry into the study, 32 patients had received chemotherapy, and most patients (41/45) had contrast enhancement of their tumors on x-ray CT. Glucose use in the tumor was compared with that of the contralateral side. A ratio of 1.4:1 of tumor to nontumor was found to be the median level of glucose use, and patients were divided into two groups with regard to their survival (Figure 3).[69] Patients having tumors with high metabolism—ratios greater than 1.4—had a mean survival of 5 months; those with tumors having a ratio of less than 1.4 had a mean survival of 19 months. The histologic grade of tumors also correlated with survival, with the patients with grade III tumor surviving longer than those with grade IV. The PET findings, however, were superior to histologic variables in predicting ultimate prognosis. Thus, patients with metabolic tumor ratios greater than 1.4 had short survival times, regardless of their histologic grade.

Measurements of glucose metabolism by PET in cerebral neoplasms are useful in identifying the grade of tumor with respect to malignancy in the glioma series and in determining the prognosis for a patient. In addition, measurements of glucose metabolism support the concept put forth by Warburg nearly 60 years ago that accelerated glycolysis is a characteristic of tumors and is proportional to their degree of malignancy.[52]

Cerebral Blood Flow and Oxygen Use

Several investigators have examined the cerebral blood flow and oxygen use of cerebral neoplasms.[68-71] Despite the

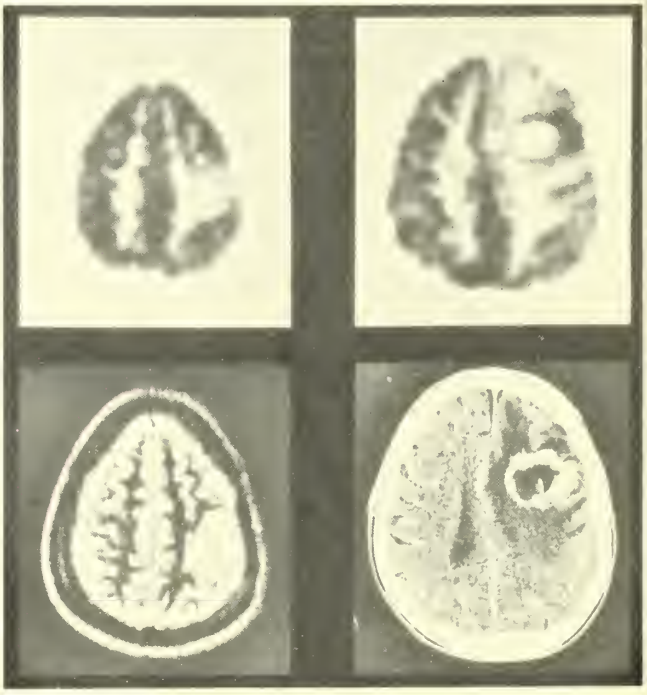

Figure 2.—High- and low-grade gliomas are differentiated with positron emission tomographic (PET) determinations of glucose metabolism. The upper row of images shows PET studies of glucose metabolism using [^{18}F]fluorodeoxyglucose (FDG), the bottom left is a magnetic resonance imaging (MRI) study, and the bottom right is an x-ray computed tomographic (CT) study after the administration of iodinated contrast material. The patient depicted in the left column has a low-grade (grade II) glioma of the frontoparietal cortex. Surrounding edema is obvious in the MRI scan. The glucose metabolism of this lesion is low and comparable with that of normal white matter. In contrast, the patient whose studies are depicted in the right column shows the appearance of a high-grade (grade IV) glioma in the frontal lobe. The x-ray CT study of this patient shows a central area of low attenuation surrounded by a low-density area that extends throughout the frontal and into the parietal lobe. The latter distribution is consistent with tumor-associated edema. The FDG-PET study of this patient shows a central area of low or absent metabolic activity consistent with tumor necrosis and a surrounding area of high metabolic activity comparable with that of the normal grey matter and consistent with a highly malignant glioma. Surrounding the hypermetabolic zone is a more general reduction in glucose metabolism in the adjacent frontal cortex, which may represent the effects of edema or pressure effects, or both, directly exerted by the tumor. Thus, while the site of these lesions, their attendant edema, and mass effects can be shown by x-ray CT or MRI, information about the histologic nature of tumors is, in addition, provided by measurements of glucose metabolism with PET.

fact that cerebral gliomas have an accelerated rate of the use of glucose, reflecting their high glycolytic rate, they have decreased oxygen use. These tumors shift away from oxidative metabolism (which supports the prediction of findings in animals) where fast-growing tumors have augmentation of the Embden-Meyerhof pathways despite adequate oxygen availability. These studies have included the measurements of local cerebral blood flow, oxygen use, and oxygen extraction fraction in cerebral gliomas and metastatic brain tumors using ^{15}O-labeled compounds and PET (Figure 4).[68-71] These results have been discussed by Beancy and associates with respect to cerebral and systemic tumors.[73,74] In addition, these authors found that surgical decompression of brain tumors reduces the abnormalities in blood flow and oxygen use, indicating a direct physiologic correlation with beneficial effects for this type of surgical treatment.

The stoichiometry of brain tumors indicates that they have enhanced glycolysis (increased glucose use), normal-to-mild reductions in cerebral blood flow but decreased cerebral oxygen use despite an adequate supply of oxygen in the arterial blood (low oxygen extraction fractions). These data are important in selecting the appropriate radiation or chemotherapeutic regimens for patients with tumors, particularly as they can be measured in individual patients to determine if their tumors are existing in oxygen-rich or oxygen-deprived environments. The use of PET to monitor the effects of therapeutic modalities while doing stoichiometric studies of the tumor can and should continue to play a significant role in the future understanding of the response of tumors to the maneuvers.

Blood-Brain-Barrier Alterations

The initial PET studies of intracerebral neoplasms used gallium 68 (^{68}Ga)-labeled edetic acid to localize altered blood-brain-barrier sites.[75-78] These studies and others using rubidium 82 (^{82}Rb) resulted in discrete and precise localization of such tumors that correlated closely with iodinated contrast-enhanced x-ray CT images in the same patients.[79] Such studies have provided a quantitative model for calculating molecular diffusion rates in and near tumors.[78]

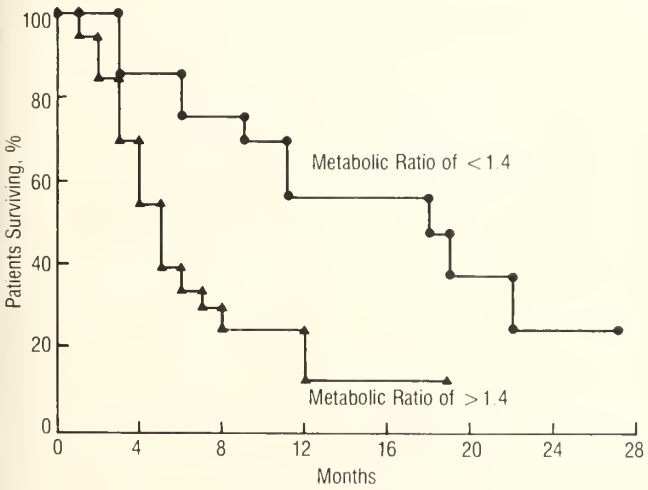

Figure 3.—Glucose metabolism is correlated with prognosis in patients with high-grade gliomas. The ratio of glucose metabolism in tumor relative to the contralateral brain tissue is termed the metabolic ratio. Patients having tumors with ratios greater than 1.4 had a mean survival of 5 months, whereas those with tumors having ratios of less than 1.4 had a mean survival of 19 months (from Patronas et al[67]; reproduced with permission).

Yen and associates used ^{82}Rb to examine patients with cerebral gliomas and intracranial metastases.[80] They showed the advantages of using this isotope, which are related to the increased mean residence time for rubidium relative to iodinated compounds, in addition to the rapid clearance of rubidium from the blood, which diminishes its recirculation. These authors concluded that ^{82}Rb imaging was more sensitive than contrast CT in detecting blood-brain-barrier alterations because of its higher distribution volume and smaller molecular size, making the penetration of minimal blood-brain-barrier defects possible.

Rubidium 82 has also been used to examine the effects of steroids and whole brain irradiation on blood-brain-barrier function.[81] It has been suggested that steroids decrease the permeability of tumor capillaries to small hydrophilic molecules, including some chemotherapeutic agents, and that steroid pretreatment prevents abrupt increases in tumor capillary permeability after cranial irradiation. Within 24 hours of administration, giving high doses of methotrexate results in alterations in the blood-brain barrier, as shown with the use of rubidium 82, and widespread depressions of glucose metabolism as determined with the use of fluorodeoxyglucose.[82] These alterations of cerebral glucose metabolism were associated with changes in neuropsychologic performance, which were identified in the absence of systemic methotrexate toxicity.[83]

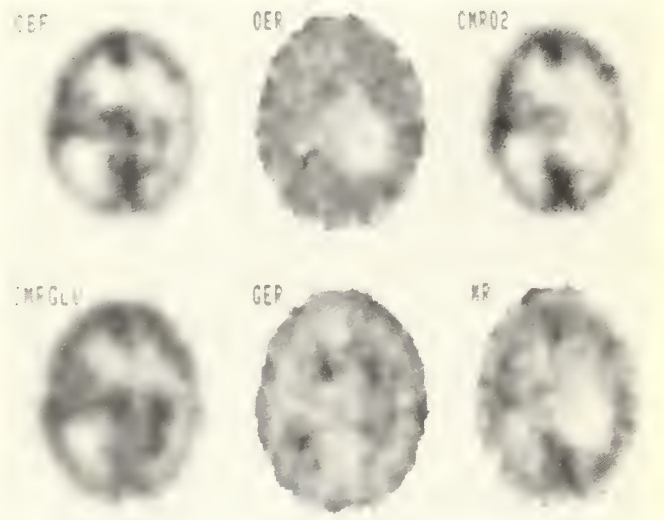

Figure 4.—Tumor stoichiometry was done in a patient with a high-grade cerebral glioma located in the depth of the right cerebral hemisphere. This patient was evaluated with positron emission tomography to determine cerebral blood flow (CBF), oxygen extraction ratio (OER), oxygen use ($CMRO_2$), glucose metabolism (CMRGLU), glucose extraction ratio (GER), and metabolic ratio (MR) of oxygen to glucose use. Blood flow is modestly but heterogeneously elevated in the tumor and suppressed in overlying cortical zones. Both oxygen use and extraction are severely reduced in the tumor itself, and the latter is moderately reduced in the overlying cortex. Glucose metabolism is increased in these lesions, as is typical of high-grade gliomas, but suppressed in overlying cortex, probably owing to edema and pressure effects. Glucose extraction is somewhat increased in the lesion, but the ratio of glucose to oxygen use is low. This latter finding is consistent with the finding of accelerated glycolysis in high-grade gliomas despite the adequate availability of oxygen, evidenced by the low extraction fraction of this lesion. Such a battery of studies in an individual patient permits the determination of the biochemical signature of lesions, such as cerebral gliomas, and the characterization of the biochemistry that underlies their growth and response to therapy. Combined studies such as these may prove critical in understanding the pathophysiology of tumor growth and may predict optimal approaches to their treatment (from Lammertsma et al[69,70]; reproduced with permission).

Amino Acid Incorporation

The initial use of [^{11}C]L-methionine with PET was reported in 1983 by Bergström and colleagues in a single patient with an anaplastic glioma.[83] Since then, amino acid uptake has been used by this group to identify, for biopsy placement, the site of low-grade gliomas that have minimal changes in blood-brain-barrier permeability or glucose use (Figure 5).[83] In addition, investigators at Johns Hopkins University have used [^{11}C]L-methionine and PET to evaluate brain tumors in children. These studies are done with methionine PET studies before and after a loading dose of a competing nonradioactive amino acid, such as L-phenylalanine, 100 mg per kg. The investigators noted a focal increase in the transport of methionine in all cases of pediatric astrocytomas and in one case of ependymoma.[84] Phenylalanine suppresses methionine uptake by the tumor, but the suppression is greater in surrounding tissue altered by radiation gliosis or edema. Thus, preloading with an amino acid that competes for the neutral amino acid carrier transport system results in a more specific and easily identifiable tumor site using labeled methionine.

^{11}C-Labeled L-leucine has also been used for estimates of protein synthesis in the human brain[85] and in cerebral tumors (Figure 6). Because protein synthesis is enhanced in rapidly growing tissue, PET measurements of this process may be a sensitive indicator of tumor cell growth and, hence, of prognosis and responsiveness to therapy.

Tumor pH

The pH of cerebral tumors has been determined using weak acids, such as ^{11}C-labeled carbon dioxide and ^{11}C-labeled dimethyloxazolidinedione.[86-89] These studies indicate that there is no reduction in pH in the microenvironment of tumors. Measurements of tumors in human subjects and in animal models indicate that the tissue within and adjacent to cerebral neoplasms has a normal or a slightly alkaline pH. Measuring the tissue pH with PET seems a useful concept because it may provide clinically relevant information about the regional acid-base state and metabolism, which may have therapeutic implications for the selection of chemotherapeutic agents and radiation therapy in patients with cerebral tumors.[88]

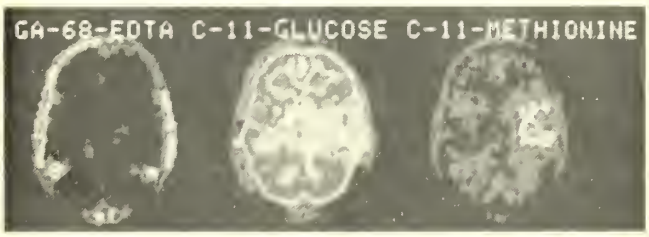

Figure 5.—The blood-brain-barrier integrity, glucose metabolism, and amino acid uptake are shown in a low-grade cerebral glioma. This patient has a low-grade glioma situated at the same site as that of the patient described in Figure 4, namely, deep in the right hemisphere. Blood-brain-barrier integrity is unaltered by this lesion, as evidenced by the absence of extravasation of gallium 68 edetic acid (EDTA), seen in the left image. Glucose metabolism is reduced by administering carbon 11-labeled glucose. Amino acid uptake of the tumor is high compared with surrounding brain, as shown by carbon 11-labeled L-methionine. Such studies indicate that the uptake of compounds such as amino acids may be useful in identifying the sites of viable tumor, particularly as a means of planning the optimal site of biopsy for such deep lesions in situations where contrast enhancement, as determined by positron emission tomography or x-ray computed tomography, is minimal and uninformative (from Bergstrom et al[85]; reproduced with permission).

Ligands

The properties of tumor receptors and the ability to measure these receptors with radioisotope-tagged ligands are areas of active research. This process can be simply extended to PET for determining the receptor properties of human tumors measured externally with a PET instrument. ^{11}C-Labeled ligands for peripheral benzodiazepine receptor complexes (for example, PK 11195), have already been developed and should be but one of several possible radiopharmaceutic approaches to understanding the cell-surface receptors of tumors systemically and in the brain.[13,90,91]

Similarly, dopamine receptors have been visualized in pituitary adenomas using PET and ^{11}C-labeled *N*-methylspiperone.[92] Patients were studied before and after haloperidol pretreatment to identify whether this compound would have significant blocking effects for dopamine receptors in pituitary adenomas. The tumor with the greatest uptake of the ligand and the greatest blocking effect from haloperidol pretreatment was in a patient with a hormonally active prolactinoma. Muhr and co-workers concluded that dopamine-receptor binding can be identified in pituitary tumors in vivo and that this technique can be useful in understanding not only the neuropharmacology of these tumors but also the varying response of prolactinomas to dopamine agonists.[92]

In addition to using PET to identify the tumor cell-surface receptors, it is also possible to examine chemotherapeutic

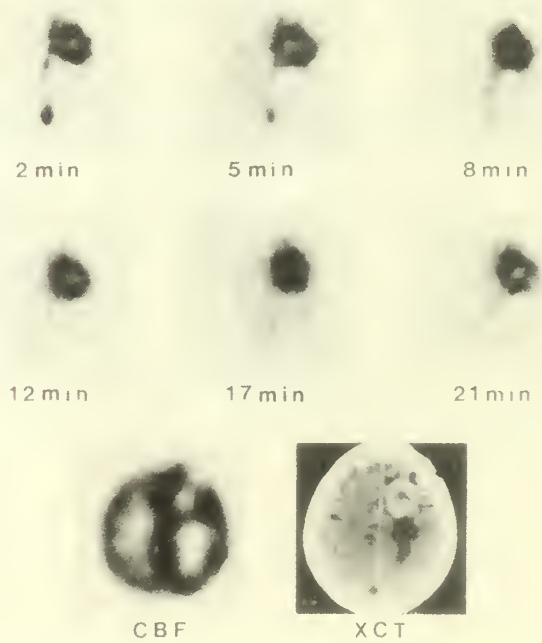

Figure 6.—Protein metabolism is shown in a high-grade (grade IV) cerebral glioma. The upper 6 images show the time course of uptake of [^{11}C]L-leucine in the brain of a patient with a right frontal grade IV glioma. The bottom images show cerebral blood flow (CBF) measured with positron emission tomography and iodinated contrast-enhanced x-ray computed tomography (XCT). The x-ray CT image shows two contrast-enhanced adjacent rings with central low attenuation characteristics. Posterior to these lesions is an area of low attenuation that extends into the white matter of the centrum semiovale. The cerebral blood flow study shows high flow in the areas of x-ray CT contrast enhancement with low or absent flow in the central zone. [^{11}C]Leucine uptake is higher in this lesion than in the normal adjacent brain. It shows a large ring pattern with a central zone of low uptake. Determinations of protein synthesis and amino acid uptake should parallel characteristics of tumor growth and may prove to be important variables for characterizing such growth in response to therapeutic interventions.

agents that have been labeled with positron-emitting isotopes. An example of this approach is typified by the use of ^{13}N-labeled cisplatin[93] or ^{11}C-labeled carmustine (1,3-bis-[2-chloroethyl]-1-nitrosourea; BCNU), a lipophilic alkylating agent.[94] Using [^{11}C]carmustine, Tyler and associates were able to directly compare the pharmacokinetics of intravenous versus superselective intra-arterial administration of the compound in patients with recurrent gliomas. Intra-arterial administration of the compound achieved concentrations that were, on the average, 50 times higher than those achieved with a comparable intravenous dose. The authors concluded that the degree of early metabolic trapping of carmustine in tumors correlated with their clinical response to this form of chemotherapy. Although the use of radiolabeled receptor ligands and labeled chemotherapeutic agents has yet to provide definitive information about the pathophysiology of cerebral neoplasms, these agents represent the tools available to neuro-oncologists for the study of these neoplastic processes. When these data are combined with the stoichiometric information derived from studies with blood flow, blood volume, metabolism, protein synthesis, and pH, they provide a broad set of biochemical and physiologic variables that characterize the natural history of tumors and their response to therapy.

Adjacent and Distant Effects of Tumors as Determined With Glucose Metabolism

All investigators who have examined tissue adjacent to cerebral neoplasms have noted reductions in glucose metabolism,[41,61,95] blood flow, and oxygen use.[73] With regard to glucose metabolism, 54 of 59 patients (92%) studied with PET had such reductions.[41,61,95] Overall metabolic rate reductions for glucose in peritumoral edema were 48% ± 15%. The metabolic rate reduction was proportional to the total volume of the tumor and its edema and to the magnitude of attenuation suppression measured by x-ray CT in edematous tissue. There was no correlation between the reduction in the metabolic rate in edematous tissue and tumor grade, tumor metabolic rate, tumor enhancement (with iodinated contrast on x-ray CT), the severity or duration of neurologic symptoms, the history of seizures, or the use of steroids or other anticonvulsant medications.

A wide range of destructive processes in the brain (for example, cerebral infarction) have been shown by PET to cause distant effects presumably due to the disconnection of afferent and efferent pathways traversing the site of tissue damage.[34] Cerebral neoplasms also show this phenomenon. Distant reductions in metabolism, typically linked with identical reductions in blood flow, have been measured for glucose and oxygen use.[41,64,69,95] In patients with deep cerebral gliomas, suppression of glucose metabolism in the overlying ipsilateral cortex has been identified.[41,64,66] The reverse situation is also true, and cases have been reported wherein cortical tumors have resulted in a suppression of metabolic rates in the ipsilateral thalamus of approximately 20%. When blood flow has been combined with metabolic measurements, it has been found that reductions of a similar degree in both variables occur in a coupled fashion.[69] This is good evidence that these distant effects are not a product of ischemia, but rather reflect functional disconnection of one structure from another.

Decreases in glucose metabolism for the cerebellar hemisphere contralateral to supratentorial gliomas have also been reported[29,34] and have a pattern similar to that seen in patients with cerebral infarctions. In 21 such patients with supratentorial tumors, 12 had contralateral suppression of cerebellar metabolism ranging in magnitude from 8% to 34%. All of these patients had either a tumor or tumor edema involving the sensorimotor frontoparietal cortex with or without thalamic involvement. In the nine patients without contralateral cerebellar metabolic suppression, the tumors were at sites other than those involving sensorimotor cortex. The degree of cerebellar metabolic abnormality was related to the size of the tumor, to the presence of hemiparesis, and possibly to the rapidity of growth of the tumor. The changes in cerebellar metabolism did not seem to correlate with the duration of symptoms. The interesting phenomenon of cross-cerebellar flow and metabolic suppression represents an example of the ability of PET functionally to show anatomic connections between the cerebral hemispheres and the posterior fossa. Similar results have been described in patients with other destructive lesions of the cerebral hemispheres as noted earlier.

Tumor Recurrence Versus Radiation Necrosis

Radiation necrosis can occur in patients receiving 50 to 60 grays (5,000 to 6,000 rads) of radiation to the brain. Neurologic signs and symptoms often occur months after therapy is completed. With the emergence of new or recurrent symptoms referable to the same site as before tumor therapy, it is virtually impossible for clinicians to differentiate between the two inciting processes. Both radiation necrosis and tumor recurrence are associated with mass effect, edema, and contrast enhancement using structural imaging modalities such as x-ray CT or MRI; these modalities have been of little help in differentiating the two disorders.

Because necrotic brain does not metabolize glucose, it has extraordinarily low metabolic rates and provides for relatively easy differentiation from recurrent high-grade tumor when measurements are made with fluorodeoxyglucose and PET (Figure 7). Recurrent high-grade tumors typically show glucose use with values similar to or in excess of normal grey matter. Irradiated but nonnecrotic brain tissue has severely reduced glucose metabolic rates. Patronas and co-workers described this phenomenon and accurately predicted biopsy or autopsy results in patients where this differential issue was of clinical importance.[63] Two patients had radiation necrosis, and three had recurrent tumors in this series.

In a separate and larger series by the same group, glucose metabolism was examined in 95 patients who were referred for the consideration of tumor recurrence versus radiation necrosis. Of these patients, 10 were accurately diagnosed as having radiation necrosis and 85 were accurately diagnosed as having recurrent tumor.[96] Similar results have been obtained in other laboratories.[97] One study of 34 patients had an overall accuracy of 84% in differentiating tumor recurrence from radiation necrosis. This last study, however, differs somewhat from the other protocols in that many of these patients had brachyradiation therapy rather than conventional external-beam therapy.[98]

The value of being able to determine noninvasively whether new signs and symptoms in a previously treated tumor patient represent recurrent tumor or radiation necrosis includes the obvious advantage of avoiding biopsy in every patient. Radiation necrosis can usually be managed medically with drugs to reduce edema. Evidence of recurrent

tumor and knowledge of its estimated histologic grade from PET can dictate the strategy for future therapy, including repeat surgical resection or guided biopsy when clinically indicated.

Functional Activation of the Brain for Surgical Planning

Increases in neuronal activity associated with behavioral tasks can be determined using PET by defining blood flow or glucose metabolism.[32] As noted earlier, the planning of surgical therapies for patients with brain tumors involves avoiding areas that are critical to the performance of key behavior tasks such as movement, audition, language, and vision (Figure 8). By combining structural images from MRI or x-ray CT with metabolic or blood flow activation studies and PET, it is possible to identify the relation between tumor sites and adjacent or surrounding areas of functional activity. For example, consider a patient with a low-grade glioma in the posterior frontal lobe close to, but not specifically invading, the motor cortex for the hand (Figure 2). On neurologic examination, the hand seems normal with only a minimal degree of clumsiness on complex testing. By measuring cerebral blood flow or glucose metabolism while the subject performs a behavioral task with the hand, it is possible to identify those cortical and subcortical structures that subserve the task in a given patient with cerebral tumor. Combining the distribution of the tumor identified from MRI, x-ray CT, or PET (the last using metabolism or tracers for cell-surface receptors such as those for peripheral benzodiazepine receptors), the three-dimensional spatial relation between the neuronal network subserving the motor task and the tumor can be simultaneously identified. With this information, it is possible to plan the extent of the operation, the site of the craniotomy, and the strategy for the resection. Such approaches should make surgical tumor treatment safer, resulting in lower morbidity as reflected by reduced neurologic deficits postoperatively.

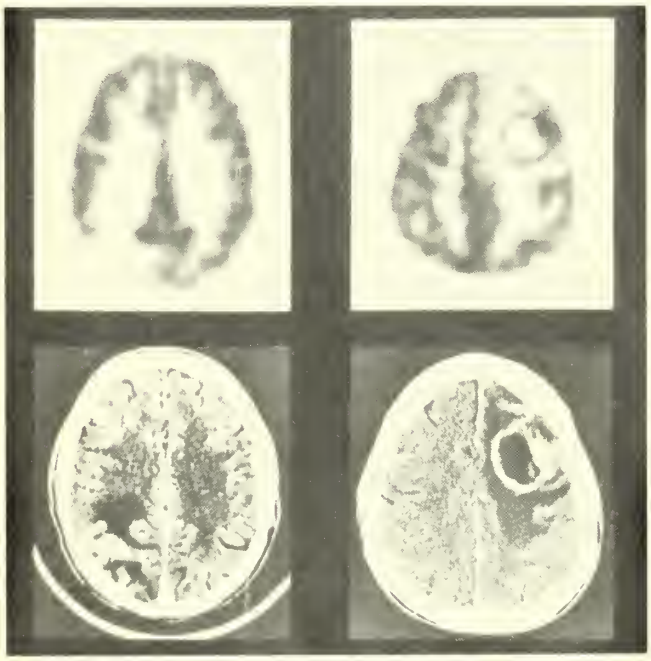

Figure 7.—The upper level of images is from positron emission tomographic studies of glucose metabolism using [^{18}F]fluorodeoxyglucose, whereas the bottom images are x-ray computed tomography (XCT) scans after iodinated contrast enhancement. The patient in the left column has radiation necrosis, and the patient on the right has a recurrent high-grade glioma. Both x-ray CT studies show contrast enhancement and surrounding low attenuation consistent with edema. A differential diagnosis based on x-ray CT alone, therefore, would not be possible, and such a decision would typically require a surgical biopsy. Glucose metabolism is low, or absent, in zones of radiation necrosis, as shown by the patient on the left. Recurrent tumor is evidenced by metabolism that equals or exceeds that of normal grey matter, as shown by the patient depicted in the right column. The patient on the right has a ring area of hypermetabolism surrounding a central zone of tumor necrosis. The reduction in glucose metabolism in the overlying frontal cortex is probably due to edema or pressure effects, or both.

Clinical Strategies for Treating Malignant Brain Tumors

DONALD P. BECKER, MD*: The prognosis is poor for patients with primary malignant astrocytomas (Kernohan classification grades III and IV and World Health Organization classification anaplastic astrocytoma and glioblastoma) despite surgical excision and radiation or chemotherapy (or both). Malignant gliomas account for about half of the 9,000 new cases of primary brain tumors reported annually in the United States.[99] These infiltrative tumors progress rapidly. Resection followed by external-beam irradiation remains the standard treatment, yielding mean survival times of about 35 weeks from the time of the operation.[100,101] It is noteworthy that about 80% of patients have recurrence of the tumor within 2 cm of the initial tumor margin.[102] Some workers have therefore suggested that improved local control could lead to longer survival times.

The factors that have an important influence on patients'

*Professor of Surgery, Division of Neurosurgery, UCLA School of Medicine.

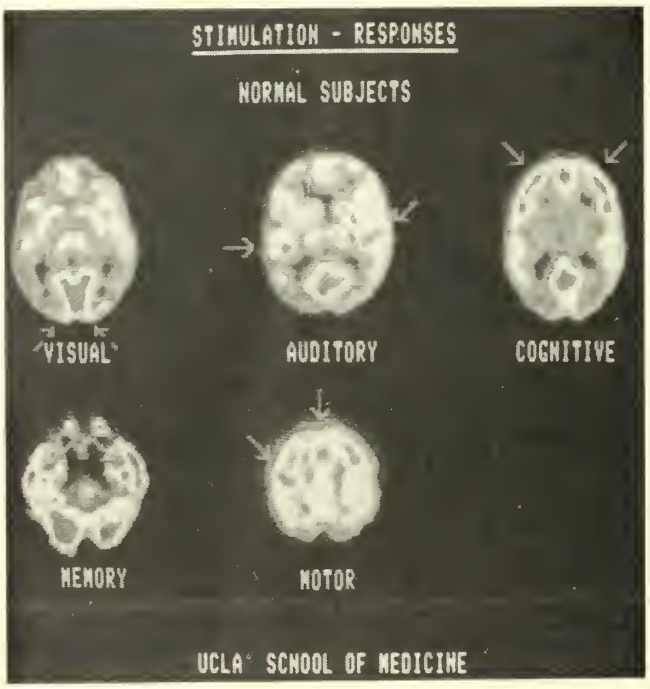

Figure 8.—Glucose metabolic responses are shown of normal subjects performing behavioral tasks. The arrows indicate areas of high metabolic rates indicative of increased neuronal activity. Normal patterns of metabolic responses to behavioral tasks can be used to map critical sites of functional neural networks in patients with cerebral tumors to avoid these areas during tumor resection, as in the two patients whose positron emission tomographic studies are shown in Figure 2. Both lesions are at or near the sensorimotor strip. Both of these patients have minimal signs of corticospinal tract dysfunction. A behavioral mapping study to examine displacement and position of the functional motor cortex (as seen in the "motor" image of this figure) would be useful in avoiding these critical areas during resection of the cerebral neoplasms (from Phelps and Mazziotta[32]).

survival with malignant gliomas include age, duration of symptoms, preirradiation performance state, tumor histology, accessibility to resection, extent of resection, radiotherapy, and a previous diagnosis of a low-grade glioma. Patients with gross total resections live longer than those with partial resection, and patients with any degree of resection live longer than those who undergo only a biopsy procedure. Also, patients with anaplastic gliomas in whom there was a history of low-grade glioma live considerably longer after the diagnosis of anaplastic glioma than do patients in whom anaplastic gliomas currently arose de novo. Some authors have reported a difference in survival of only 19 weeks in patients who have undergone biopsy to 76 weeks in patients with gross total resections. Age is a strong predictor of survival, with patients in the 18- to 44-year-old group having a median survival of 107 weeks in comparison with patients older than 65 years who have a median survival of only 23 weeks.

Recently thallium 201 (single photon emission CT) scans have been shown to correlate with tumor histology in patients with gliomas. A thallium index was developed based on the ratio of thallium 201 uptake in the tumor versus the nonneoplastic homologous area of brain. A thallium index of 1 represented no uptake. In these patients, an index of 1.5 or less showed a 90% or higher accuracy of predicting which patients will have low-grade gliomas versus an index of higher than 1.5, where the tissue specimen almost always showed a grade III or grade IV glioma. In our experience, the thallium scan is more accurate than the CT or MRI scan in predicting tissue histology because it does not rely merely on a breakdown of the blood-brain-barrier blood flow, but the thallium is recognized as a potassium analogue and is actively pumped into tumor cells by sodium-potassium-adenosine phosphatase.[103]

A slight increase in the number of long-term survivors is obtained by treatment with carmustine.[104] Its full potential, however, may be limited by the delivery of high doses to the tumor site while avoiding systemic toxicity. Various attempts to increase the concentrations of cytotoxic drugs in the brain have proved disappointing. Other forms of regional treatment, including interstitial irradiation, have had some success at local control. A novel approach has recently been developed to optimize local carmustine concentrations in the region of the tumor by what has been termed "interstitial chemotherapy." A biodegradable polymer, manufactured by Nova Pharmaceutical Corporation, Baltimore, Maryland, has been formulated into a solid wafer containing carmustine in the matrix. Encouraging results were obtained in a series of preclinical studies in rats, rabbits, and nonhuman primates to establish the biocompatibility, biodistribution, and efficacy of carmustine-containing polymer wafers when implanted intracerebrally.[105,106] Phase I clinical trials have recently been completed. In the first human study administering carmustine by interstitial chemotherapy using drug-loading polymer wafers, patients with malignant gliomas, for whom surgical therapy and radiation therapy or chemotherapy, or both, were ineffective, underwent a second surgical resection and the wafers were implanted into the margins of the surgical resection. The results of this study show that this may be a safe method for delivering chemotherapy into the brain. The wafers have the advantage that they can deliver extremely high concentrations of chemotherapy into the brain while avoiding the systemic side effects of the chemotherapeutic agent. In addition, there is prolonged exposure of the tumor cells to the chemotherapeutic compounds. Further, these wafers can be loaded with various antitumor modalities, so their full potential as a delivery tool for antitumor compounds to treat brain tumors is just beginning to be explored.

There has also been increasing interest in the impaired humoral and cellular immune function in patients with primary brain tumors. Recently there has been interest in the development of immune modifiers that stimulate the host immune system in patients with malignant brain tumors. Regimens using levamisole hydrochloride, poly IC, interferon, picibanil, or bacillus Calmette-Guérin vaccine have been attempted with limited success. A biologic response modifier, ImuVert (Cell Technology, Inc, Boulder, Colorado), prepared from the bacterium, *Serratia marcescens*, has recently been developed. ImuVert is known to stimulate the activity of human natural killer cells in vitro, using a standard chromium-release cytotoxicity test. In addition, it also causes the release of interleukin 2, interferon, and tumor necrosis factor and stimulates lymphocytic activated killer cells as well as antitumor macrophages. Because of the broad-based immune stimulation of ImuVert, clinical trials have recently begun testing its effects in patients with high-grade gliomas.

It is hoped that future treatment modalities may be able to convert this universally fatal disease to a chronic disease process that can be controlled. Controlling recurrence at the surgical margins and maintaining static growth of the tumors by stimulating patients' immune systems might lengthen survivals in these patients. Combinations of various therapies based on increasing knowledge of the biologic behavior of these tumors are currently being designed. A better definition of the surgical margins is critically needed, and a way to deliver antitumor compounds successfully across the blood-brain barrier specifically to tumor cells will improve dramatically the effectiveness of current therapeutic modalities.

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Biomedical Science

Lovastatin Use and Muscle Damage in Healthy Volunteers Undergoing Eccentric Muscle Exercise

CHRIS S. REUST, MD; STEVEN C. CURRY, MD; *and* JAMES R. GUIDRY, PharmD, *Phoenix, Arizona*

We did a double-blind, placebo-controlled crossover study of 10 healthy young men taking no medications to determine if ingesting lovastatin is associated with more severe muscle damage after exercise. Five men in the first group took 40 mg of lovastatin daily for 30 days while those in the second group took an identical-appearing placebo. Each volunteer then walked downhill on a −14-degree incline on a treadmill at 3 km per hour for an hour. After a 2-week rest, the subjects were crossed over. Serial serum creatine kinase activity was measured immediately before and 8, 24, 48, 72, 120, and 144 hours after each treadmill session.

With each subject serving as his own control, peak mean serum creatine kinase activity (±SEM) following treadmill after lovastatin therapy was similar to that following placebo (168.4±25.8 U per liter versus 146.7±14.7 U per liter, respectively [P=.9]). With an α value of .05, we had greater than a 99% chance of detecting a difference in the rise of serum creatine kinase activity of 200 U per liter between groups. Our data suggest that lovastatin is not an independent risk factor for developing exercise-induced muscle damage using this model of exercise in our study population.

(Reust CS, Curry SC, Guidry JR: Lovastatin use and muscle damage in healthy volunteers undergoing eccentric muscle exercise. West J Med 1991 Feb; 154:198-200)

Preclinical studies examining the safety and efficacy of lovastatin use have found the incidence of elevated serum creatine kinase (CK) activity (reflecting muscle damage) to range from 0.5% to 2% in those taking the drug.[1,2] Several reports have since described mild to moderate myopathy and overt rhabdomyolysis in patients taking lovastatin for the treatment of hypercholesterolemia.[3-9] All of these later patients had also been taking other medications, including immunosuppressive agents, other cholesterol-lowering drugs, and antibiotics.

Muscle damage, including rhabdomyolysis and myoglobinuric renal failure, can also be seen after excessive exertion. Even normal exercise is accompanied by biochemical evidence of muscle damage such as increased serum CK activity and elevated serum myoglobin and uric acid concentrations.[10] A recent report suggested that exertional myopathy may be more likely to occur in patients taking lovastatin.[11] We report a double-blind, placebo-controlled crossover study in ten healthy men to examine the ability of lovastatin to raise serum CK levels after exercise.

Subjects and Methods

Experimental subjects were ten 27- or 28-year-old nonsmoking white men who were within 20% of ideal body weight. They had no known medical illnesses and were taking no medications. Because untrained persons have greater rises in markers for rhabdomyolysis after exercise,[12-15] the volunteers were required to have not participated in any regular exercise program for at least four months before the study began.

After baseline physical examinations and routine chemistry studies, including the measurement of serum cholesterol levels and CK activity, subjects were randomly assigned to two groups of five men. Five men in group A took one 40-mg capsule of lovastatin daily, and five men in group B took an identical-appearing placebo capsule daily for a month. Both investigators and volunteers were blind as to the contents of the capsules.

At the end of the month, each subject walked downhill on a −14-degree incline at 3 km per hour for an hour on a treadmill. This was done to produce eccentric muscle contractions that have been shown to result in reproducible and more severe elevations in serum CK levels than concentric muscle exercise.[16] Blood specimens were drawn for the measurement of serum CK activity and cholesterol concentrations immediately before exercise and then for the measurement of serum CK levels at times 0 (immediately after the treadmill test), and 8, 24, 48, 72, 120, and 144 hours after the end of the treadmill exercise.

After a two-week period, the subjects were crossed over so that group A subjects took placebo and group B subjects took lovastatin for a month. Identical treadmill exercises and blood chemistry studies were then repeated.

Two-tailed, paired t tests were used to compare serum cholesterol concentrations after placebo or lovastatin therapy with baseline values and to compare peak serum CK activity after exercise with baseline values obtained immediately before exercise. Using a doubling of the upper limits of serum CK activity and an α error of .05, ten subjects in each group provided a power of greater than .99 to detect a difference, if one existed—that is, $\beta < .01$.

Results

Baseline serum cholesterol concentrations for all subjects (5.1 ± 0.55 mmol per liter [195.6 ± 21 mg per dl]; mean ± standard error of the mean [SEM]) did not fall signifi-

From the Departments of Medicine (Drs Reust and Curry), Medical Toxicology (Dr Curry), and Pharmacy (Dr Guidry), Good Samaritan Regional Medical Center, Phoenix, Arizona.

Reprint requests to Steven C. Curry, MD, Department of Medical Toxicology, Good Samaritan Regional Medical Center, 1130 E McDowell Rd, Phoenix, AZ 85006.

ABBREVIATIONS USED IN TEXT

CK = creatine kinase
SEM = standard error of the mean

cantly after placebo therapy (decline of 0.85 ± 0.58 mmol per liter [32.5 ± 22.4 mg per dl]; $P = .18$). After taking lovastatin for a month, serum cholesterol concentrations fell by a mean of 1.51 ± 0.43 mmol per liter (58.2 ± 16.4 mg per dl; $P = .006$), indicating that subjects were compliant in taking their medication.

Following treadmill exercise after lovastatin was taken, mean serum CK values rose from a baseline of 113.6 ± 14.9 U per liter to a peak of 168.4 ± 25.8 U per liter ($P = .0001$). Following treadmill exercise after placebo was taken, CK values also rose significantly from a pretreadmill mean of 100.7 ± 13.4 U per liter to a mean peak of 146.7 ± 14.7 U per liter ($P = .02$). There was no statistical significance in the degree of rise of CK activity after lovastatin use as compared with placebo ($P = .9$). The order of drug administration (lovastatin versus placebo) appeared to have no influence on peak CK activity, indicating that a training effect from the first treadmill exercise did not influence the results obtained after the second exercise. Figure 1 represents the mean serum CK values at indicated times following the treadmill test. Because serum CK activity in individual subjects peaked at different times, the mean values reflected on the graph are not identical to those used for statistical analysis.

Discussion

The literature contains several reports of muscle damage occurring both spontaneously and in response to exercise in patients taking lovastatin.[1-9,11] Most of these patients had

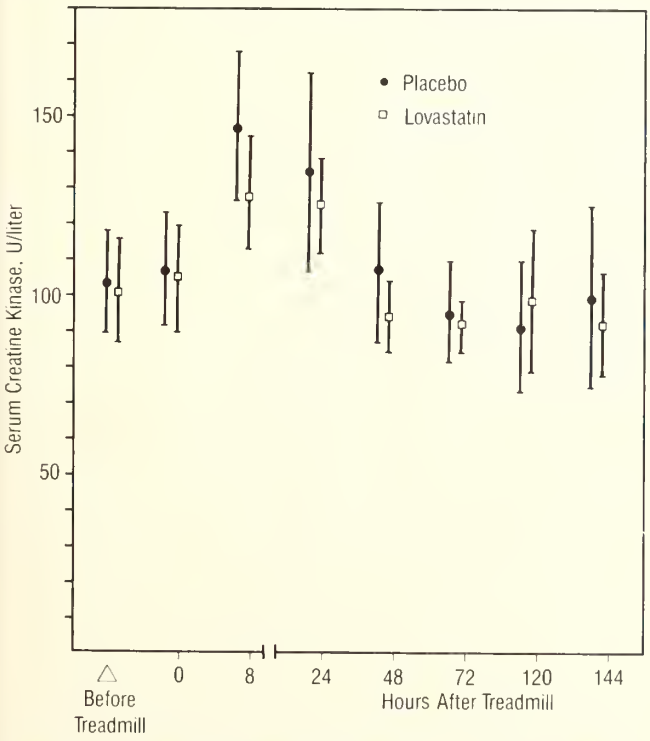

Figure 1.—In this graph of serum creatine kinase (CK) activity versus time, the pretreadmill values represent serum CK activity immediately before exercise and all other values are at times after the treadmill exercise was terminated. The values represent the mean ± a standard error of the mean.

been taking other medications as well, including other cholesterol-lowering drugs, immunosuppressive agents, and antibiotics. To our knowledge, this is the first study evaluating the effects of lovastatin as an independent risk factor for exercise-induced muscle damage.

We could not demonstrate a greater rise in serum creatine kinase activity induced by exercise in subjects taking lovastatin than in those taking placebo. Although our study population was biased toward a young, healthy cohort, age has not been reported to be a risk factor for exercise-induced rhabdomyolysis.[17] All other confounding variables such as race, sex, drug use, and training were controlled for.[17,18]

Serious muscle damage following exercise is commonly accompanied by hundreds-fold to thousands-fold elevations in serum CK activity.[19] With an α value of .05 in our study population, we had greater than a 99% chance of detecting a difference in the rise of serum CK activity of as little as 200 U per liter in response to exercise when lovastatin was taken as compared with placebo, if such a difference existed.

In a study of five normal untrained volunteers (two men, three women) ranging in age from 23 to 34 years, Newham and colleagues were able to show a greater rise in serum CK activity following identical eccentric exercise[16] than we found in our subjects. The smaller degree of rise we found may have been due to the fact that our subjects were in better physical condition. Our volunteers all were medical house staff who, although not involved in any regular exercise program, were accustomed to walking up and down stairs almost daily. Most likely, more severe eccentric exercise, such as longer treadmill walks, would result in greater CK rises in our subjects.

It could be argued that more severe exercise-induced muscle damage should have been induced in our patients to reflect CK rises typically seen after prolonged vigorous exercise. Without knowing the risk of severe exercise-induced muscle damage with lovastatin use, we did not want to produce more severe muscle damage for fear of exposing volunteers to undue risk. Furthermore, we did show significant and reproducible rises in serum CK activity reflecting muscle damage from exercise, and these were no greater after lovastatin use.

Although patients taking lovastatin often have coexisting factors predisposing them to rhabdomyolysis—such as poor nutrition, heart failure, alcoholism, and the use of other pharmaceutical agents—our data suggest that lovastatin is not an independent risk factor for the development of exercise-induced muscle damage in our study population. The possibility still exists that persons who may be more susceptible to exercise-induced myopathy or who undergo more severe exercise might have a greater degree of muscle damage when taking lovastatin. Our model may prove useful in determining which coexisting conditions increase the risk of exercise-induced rhabdomyolysis in such patients.

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POEM WITHOUT A NAME

Caminante, no hay camino
Se hace camino al andar.

You come to me and say you're sorry
for the trouble you've brought to me:
the teacher whose changed face now frightens
children, the wife whose keys went through her cheeks*
so a child now lets her in,
the one who is missing who you will never bring to me,
and your own returning there to all these things.

So you must, you say, and I must
stay here and wonder who will bring which one of these
(of you) to me one day in this office where
I work and can only keep in my mind words
to keep the pictures out, words another doctor said,

(your brother, dead):
"It is no longer different for us now—
our work will not protect us long from grief
or love."

Remember, you did not bring
these things to me I looked
for you as I will look
for you and look

*It is a common practice during interrogation in some Latin American countries for a person's housekeys to be passed through the cheeks.

FRANK PAIZ
Berkeley, California

Radiologic Case

An 18-Year-Old With Acute Testicular Pain

JONATHAN M. LEVY, MD; CARY J. STEGMAN, MD; EDWARD R. KATZ, MD; *and*
SHIRLEY WAGNER, CNMT, RT(N), *Scottsdale, Arizona*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

An 18-year-old boy had the sudden onset of left testicular pain, unrelated to trauma. His left testicle was exquisitely tender to palpation. There was no mass. He was sent for a radionuclide scan, an early image of which is shown as Figure 1.

What is the differential diagnosis?

Which of these entities is most likely, given the appearance of the radionuclide scan?

What is the treatment?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

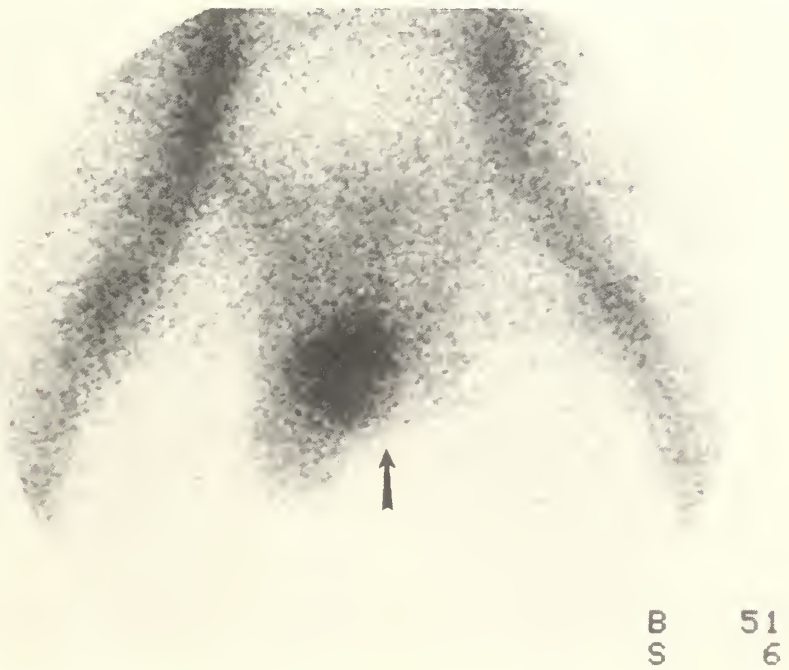

Figure 1.—A flow study is done of patient with left testicular pain. The arrow marks the median raphe of the scrotum.

(Levy JM, Stegman CJ, Katz ER, Wagner S: An 18-year-old with acute testicular pain. West J Med 1991 Feb; 154:201-202)

From the Departments of Diagnostic Radiology (Dr Levy, Dr Stegman, and Ms Wagner) and Urology (Dr Katz), Scottsdale Memorial Hospital, Scottsdale, Arizona.
Reprint requests to Jonathan M. Levy, MD, Department of Diagnostic Radiology, Scottsdale Memorial Hospital, 7400 E Osborn Rd, Scottsdale, AZ 85251.

DIAGNOSIS: Torsion of the testicle

In young patients with acute testicular pain and no antecedent trauma, the differential diagnosis includes torsion of the spermatic cord, torsion of the appendix testis, and epididymitis. It is important to differentiate these three disorders because of differences in treatment.

Torsion of the appendix testis produces pain often localized to the upper pole of the testis. It is usually self-limited, though secondary hydrocele formation is common. Atrophy of the appendix testis and resolution of the symptoms are the most common outcome. Epididymitis is usually due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis* in young, heterosexual men, while *Escherichia coli, Pseudomonas* species, and gram-positive cocci are common in homosexual men and young boys. Therapy for epididymitis consists of appropriate antibiotics and avoidance of surgery.

Torsion of the testis requires early treatment to salvage the testicle. Irreversible damage can occur after a few hours, resulting in testicular atrophy. While many authors have advocated early surgical treatment in all suspected cases, others suggest doing Doppler ultrasonography or radionuclide imaging, or both, to confirm or exclude the diagnosis. On ultrasonograms, patients with testicular torsion have no Doppler signal in the involved testicle, indicating a lack of intratesticular flow. Ultrasonography can often make the diagnosis quickly, and the addition of color Doppler equipment should make this procedure the primary diagnostic modality in the future. Radionuclide scans will then be done in patients for whom the Doppler study results are normal or indeterminate.

Since 1973 radionuclide scanning has been used to differentiate testicular torsion from inflammation. Scans are optimally performed with small field-of-view gamma cameras and high-resolution parallel hole collimators. The patient is placed in a supine position beneath the collimator, with the penis taped back over the symphysis pubis. An intravenous bolus of 10 mCi technetium Tc 99m pertechnetate is administered, and images are obtained over the scrotum at 2-second intervals for 60 seconds. Static images are then obtained immediately and at 5 and 10 minutes after injection. If there is a question about lateralization, images can be obtained with a cobalt 57 marker over the median scrotal raphe.

Testicular torsion is characterized by a lack of radionuclide accumulation (photopenia) over the affected side (Figure 1). In inflammatory processes, just the opposite occurs, with increased radionuclide uptake due to the inflammatory process. This provides a reliable differential diagnosis. Torsion of the appendix testis most often produces a normal scan, though minor asymmetry with decreased perfusion over a portion of the involved testicle has been described.

The treatment of testicular torsion classically consists of surgical detorsion and bilateral fixation of the testes (orchiopexy). Bilateral fixation is done because of the high incidence of contralateral torsion. Manual detorsion can be done in cases of acute torsion to avoid testicular infarction, but this should be followed by surgical treatment in all cases. Our patient had bilateral orchiopexy and is doing well with no sequelae.

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Epitomes

Important Advances in Clinical Medicine

Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in plastic surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Lymphedema

LYMPHEDEMA IS INCURABLE despite intensive surgical and medical efforts. Its cause is unknown. Significant swelling develops in about 1% of patients after axillary or inguinal node dissection, but not in the other 99%. A congenital predisposition may underlie the development of lymphedema.

Most patients are best treated by conservative measures, especially elastic compression stockings, weight loss, and the judicious use of diuretics.

Surgical treatment is used when enlargement of an extremity causes functional impairment. Relatively modest increases in the circumference of an extremity can represent liters of fluid, thus causing the patient to carry several kilograms of extra weight. In addition, recurrent cellulitis can be a difficult and disabling problem. These problems can be ameliorated substantially by surgical intervention.

The surgical treatment of lymphedema is divided into two approaches: physiologic (attempts to reconstruct lymphatic flow) and excisional (the removal of varying amounts of skin and subcutaneous tissue). Encouraging results with the use of lymphatic grafts, lymphatic anastomoses, and lymphatic-venous anastomoses have recently been reported. Although improvement is seen, cure is still not possible. Other operations such as the buried dermal flap and omental transposition have been generally discarded in favor of more successful approaches.

The operative procedure that provides the most consistent improvement of lymphedema with the lowest incidence of complications is extensive skin and subcutaneous excision beneath skin flaps. In a series of more than 100 patients treated by this method, about 70% have notable clinical improvement with a reduction of extremity girth of more than 50%. The more skin and subcutaneous tissue removed, the better the postoperative result.

In the future we should see improved microvascular procedures to reconstruct lymphatic flow. The key to more successful surgical approaches is likely to be earlier intervention before swelling is well established, fibrosis results, and the permanent destruction of lymphatics and their delicate valvular mechanisms occurs.

TIMOTHY A. MILLER, MD
Los Angeles, California

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Early Reconstruction of Facial Burns

MOST FACIAL BURNS are appropriately treated with local wound care and topical antibacterials and heal promptly with minimal scarring. When treated in this way, however, 5% to 10% fail to heal or do so with considerable scarring. In this instance, late reconstruction is required.

Early excision and grafting has become the standard method of treating deep burns of the nonfacial areas of the body but has not been used on deep facial burns until recently. Instead, routine, thin skin grafts were placed on granulation tissue, planning on late reconstruction. The technique of early excision and grafting shortens the hospital stay; using aesthetic units rather than small patchwork grafts improves appearance.

Obvious third-degree face burns are prepared for excision and grafting. Indeterminate face burns are treated with twice-a-day hydrotherapy and topical antibacterials for ten days. At that time the patient's face is evaluated and those aesthetic units that are judged unlikely to be healed by three weeks are scheduled for excision and grafting. The facial units are excised and porcine xenograft applied. A day or two later, the patient is returned to the operating room and a negative impression is taken over the xenograft. Thick, split-thickness grafts from the blush area are then harvested at 0.046 to 0.061 cm (0.018 to 0.024 in) in adults and proportionately thinner in children. These are carefully stitched into place and dressed with compression dressings. The dressings are removed twice a day and the grafts examined for slippage or hematomas. Pressure devices are worn until the grafts are mature.

Patients treated in this way frequently require revision of the mobile areas of the face. But the revisions are minor procedures and well tolerated by the patient and family. The large facial blocks, such as forehead and cheeks, do not require late reconstruction.

LOREN H. ENGRAV, MD
DAVID M. HEIMBACH, MD
Seattle, Washington

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Breast Implants and Cancer Detection

THE MODERN SILICONE BREAST IMPLANT was first introduced in 1963, and since then well over 2 million women in the United States (1 in 33 between the ages of 20 and 60) have had their breasts enlarged or reconstructed using this device. Uncounted more have received silicone injections for the same purpose—a procedure that has fortunately fallen into disrepute. As the median age for implantation is 32, a substantial number of women are approaching, or are well into, the cancer risk age group, thus representing a significant public health issue.

Self-detection and physical examination do not seem to be influenced by the presence of an implant. Because the silicone is radiopaque, however, mammography reliability can be diminished. Breast tissue can be hidden by the implant or compressed to a density that obscures subtle lesions.

New technology is now available by which the breast can be pulled or pinched in front of the implant, substantially improving the quality of the image and the amount of tissue viewed. This, combined with extra tangential views of obscured areas, can produce high-quality, diagnostically reliable mammograms. If a firm capsular contracture is present, this technique may not be as effective.

Are women who have had breast augmentation at risk for a delayed detection of cancer? Certainly they are theoretically at risk, and every woman should be so advised. Thus far, however, there have been no substantiated reports in the medical literature of any woman whose cancer detection was delayed because of an inability to recognize early tumors by mammography. In a study of 3,111 Los Angeles women, no delay in the detection of cancer, even with pre-"pinch" technology mammography, was found. Thus the risk, while real, would appear to be slight. The table compares these patients with all age-matched Los Angeles women without augmentation.

The American Society of Plastic Surgeons and the Society for Breast Imaging have recommended the following cancer screening program:

- *Examination.* Follow the American Cancer Society recommendations for monthly self-inspection. Annual physical examinations by physicians with experience in examining augmented breasts should be routine.
- *Mammography.* Preoperative mammograms should be obtained for women older than 35 years, every one to two years for women aged 40 to 50, and annually thereafter. High-volume screening clinics in which two quick views are taken should not be used. Mammography should be done in the same center each year by qualified mammographers who will make an effort to tailor the test to each woman. While

TABLE 1.—*Breast Cancer Stage Distribution*

Cancer Type	*All Patients in Los Angeles County, %*	*Implant Patients in Los Angeles County, %*
In situ	7.1	12.5
Local	50.2	50.0
Nonlocal	42.7	37.5

these diagnostic studies are more expensive, the low-cost screens can be unreliable and therefore worthless.

Women who have had silicone injections become impossible to examine because the silicone often forms multiple granulomatous masses, and mammograms are unreadable. These women have given up forever the ability to detect carcinoma before it has spread beyond the breast. Subcutaneous mastectomy and reconstruction should be seriously considered in this population.

GARRY S. BRODY, MD
Downey, California

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Melanoma Update

MALIGNANT MELANOMA should no longer be considered rare. With sunlight exposure as a proven etiologic factor, its rate of increase is exceeded only by that of bronchogenic carcinoma. The median age continues to be younger than 50 years and, like other neoplastic disease, melanoma is curable if detected at an early stage.

The most effective treatment of the early stages of melanoma continues to be surgical extirpation. It plays a primary role in the management of patients with stage I disease (primary melanoma) and stage II disease (recurrence of tumor in the local regional area) and a limited role in the treatment of stage III (distant metastases). Thin (< 1 mm) lesions can be cured with narrow margins (1 cm), whereas thicker lesions require 2- to 5-cm margins to decrease the risk of local recurrence. Solitary metastases to the brain, subcutaneous areas, or even lymph nodes may be suited for extirpation with a reasonably good prognosis.

The role of lymph node dissection is controversial, although data suggest a prolonged survivorship in patients with intermediate-thickness (1.5 to 4 mm) melanoma who undergo such operations. Surgical extirpation is also important in the palliation of extranodal extension to prevent the breakdown of overlying skin and soft tissues. Radiation therapy continues to be mainly palliative, especially with bony metastases.

Dacarbazine (DTIC) has been the most extensively used chemotherapeutic agent. When used as a single agent, this mode of therapy can produce response rates of 15% to 20%, largely in controlling soft tissue disease. Complete remissions are few (less than 5%) in most series.

Biologic therapy with interferon has produced responses in as high as 22% of patients with disseminated malignant

melanoma. Interleukin 2 and lymphokine-activated killer cells have also been effective: Response rates with this combination have been 20% to 30%. Treatment recommendations, therefore, include wide surgical extirpation for thick melanomas, selective regional adenectomy, and systemic therapy in some patients.

ALAN E. SEYFER, MD
Portland, Oregon

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Lower Extremity Reconstruction

LOWER EXTREMITY RECONSTRUCTIVE GOALS following severe trauma include restoring limb function, covering vital structures, and maintaining a satisfactory appearance. Techniques available to meet these goals include fasciocutaneous flaps, muscle flaps, tissue expansion, and free tissue transfer. Several new procedures have been introduced that expand treatment alternatives and permit the successful management of lower extremity soft tissue and bone defects.

Deficits involving skin and subcutaneous tissue are amenable to treatment using skin grafts, pedicle flaps with or without a defined vascular supply, and fasciocutaneous flaps. The lateral supramalleolar flap has been described recently and offers stable soft tissue coverage of the lateral malleolus. Fasciocutaneous flaps have shown their usefulness in the soft tissue reconstruction of the distal lower leg. Finally, V-Y flaps of skin and fascia based on perforating vessels entering the flap from its deep surface have been used to cover metatarsal heads, the posterior heel, and the lateral malleolus. These V-Y flaps appear reliable and are versatile in design.

Muscle and musculocutaneous flaps continue to demonstrate their versatility. The biceps femoris musculocutaneous flap has been shown to have an extended application in lesions of the anterolateral thigh. The medial gastrocnemius muscle is being used with increasing frequency to cover a threatened or exposed knee prosthesis. In addition, muscle transferred into a fibrotic cavity has been shown to increase the antibiotic concentration in that area.

Tissue expansion in the lower leg offers promise for difficult scar reconstructions but has a higher complication rate than in other areas because of problems with skin instability and the constricting deep fascial layer. When appropriate precautions are taken, however, tissue expansion for lesions below the knee can be done successfully. This involves the use of a temporary silastic bag injected with an increasing volume of a saline solution.

A recent innovation has had an effect on orthopedic and plastic surgery. After a careful corticotomy is done, bone can be slowly separated using an external fixator, with the regeneration of new bone at the osteotomy site. This permits the lengthening of bone along with the correction of angulation and rotational deformities. This technique may prove useful in the treatment of the bony deficit in osteomyelitis. The area of bone infection could be excised and the proximal bone lengthened to bridge the deficit.

Free tissue transfer using microsurgical techniques continues to expand the lower extremity reconstructive horizons. The application of the insensate scapular free flap with its thin, well-vascularized skin paddle has recently been described for the treatment of foot wounds. If this skin is carefully tailored and the excess trimmed, it is possible to achieve foot reconstruction on the plantar surface. It is now known that the fibula transferred as a vascularized graft can be osteotomized and folded on itself to provide a strong reconstruction for the tibia. A recent series reinforces the concept that osteomyelitis can be successfully managed by bone debridement, free muscle transfer, and delayed bone grafting. Free tissue transfer techniques are being applied to patients with severe peripheral vascular disease in whom the only alternative is amputation.

THOMAS R. STEVENSON, MD
Sacramento, California

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Facial Reanimation

RESTORING NORMAL facial movement after facial nerve damage is challenging. Spontaneous animation and the creation of a normal balanced smile can only be accomplished by reinnervating the paralyzed facial muscles with facial nerve fibers from the ipsilateral side. Therefore, in cases of distal seventh nerve injuries, interpositional nerve graft reconstruction is the most physiologic approach. If facial paralysis is due to intracranial injury, however, other more complicated forms of reconstruction are necessary.

Nerves from the ipsilateral side of the face can be transferred to the distal facial nerve to reinnervate the muscles. These include the hypoglossal, lingual, phrenic, greater auricular, spinal accessory, and the ansa-cervicalis. Portions of the temporalis, masseteric, and frontalis muscles can be transferred to mimic facial muscle movement. Muscle contractions after such techniques are not spontaneous, and a synthetic smile must be learned and practiced.

With the introduction of microvascular surgery, techniques have been devised to create more spontaneous facial muscle activity. A cross-facial nerve graft and a functional muscle transplantation are used in a two-stage operation to reanimate the face. During the first stage, a sural nerve graft is connected to distal branches of marginal mandibular, buccal, or zygomatic branches of the unparalyzed facial nerve. This nerve graft is tunneled subcutaneously below the lip. The free end of the nerve graft is left subcutaneous near the tragus on the paralyzed side.

Over the next six to eight months, the axons from the unparalyzed side grow across the sural nerve graft to the paralyzed side. The axonal growth can be followed by percussing over the nerve graft until an electrical shock sensation is elicited.

Once Tinel's sign is detected on the paralyzed portion of the face, the second-stage operation is done. A frozen-section biopsy of the free end of the cross-facial nerve graft is done to determine if axons have in fact grown from the unparalyzed side to the paralyzed side. If axons are present on frozen section, then the serratus anterior muscle is transplanted from the back to the face. The artery and vein to the

serratus anterior are microsurgically anastomosed to the facial artery and vein. The free end of the sural nerve graft is repaired to the long thoracic nerve of the serratus anterior muscle.

The nerve will eventually grow into the newly transplanted muscle and functionally innervate the muscle. Eventually, when the patient moves the unparalyzed side of the face, nerve impulses will travel across the nerve graft and stimulate the transplanted serratus anterior muscle. This approach can restore some spontaneous animation, particularly in patients younger than 50.

GREGORY M. BUNCKE, MD
San Francisco, California

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Soft Tissue Augmentation

IDENTIFYING A SAFE, lasting substance for use in soft tissue augmentation continues to challenge plastic surgeons and dermatologists. The most widely accepted substrate for such use is Zyderm collagen implant, approved by the Food and Drug Administration (FDA) in 1981. It is composed of enzymatically purified bovine collagen suspended in a saline solution and comes in two concentrations, Zyderm I and II. Both are recommended for the diminution of facial wrinkles, acne scars, and other depressed scars. Neither is recommended for larger defects. Correction is transient, and touch-ups are necessary every 4 to 12 months to maintain correction. Zyplast, collagen cross-linked by glutaraldehyde, was introduced in 1985. The cross-linking stabilizes the collagen against degradation but not to the extent initially hoped. Touch-ups are required on a 4- to 24-month basis. The use of Zyplast is recommended for the correction of deeper contour deficiencies. Pretreatment skin tests to determine hypersensitivity are necessary. It is now recommended the skin test be repeated at four weeks to decrease the incidence of treatment-associated hypersensitivity reactions.

There has been a continual interest in autologous fat grafting since its first use in 1893. Doubts linger as to the stability of correction beyond three to four months, and many still doubt the efficacy of this technique. Small fat grafts (4 to 6 mm in diameter) have been injected in a manner similar to the use of collagen with variable results. Supporters of the technique argue that correction lasts longer and sensitivity reactions are less severe. All agree that resorption will occur, and overcorrection and touch-ups are necessary. Inflammatory reactions, firmness, and lumpiness have been reported. In the laboratory, an adipocyte precursor with the potential to differentiate into mature adipocytes has been identified. Single-cell suspensions of these cells may show promise in creating true fat pads where injected.

Fibrel gelatin matrix implant has been approved by the FDA for the treatment of depressed scars. Reports claim an average loss of correction by 20% at two years. Local reactions have been mild, and no other adverse reactions have yet been reported. Medical grade silicone (polydimethylsiloxane) is not commercially available but continues to be used by a few practitioners. When used, proper technique is essential; there is no room for error. Technique-related problems and severe local reactions to the silicone have been reported.

JANE S. WESTON, MD
Palo Alto, California

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Maxillofacial Trauma

THE DIAGNOSIS, management, and treatment of complex craniomaxillofacial trauma are challenging for plastic and reconstructive surgeons. Maxillofacial trauma is usually considered a phenomenon of youth, but current population trends indicate the average age is increasing. There is a 50% longer median hospital stay in patients older than 65 compared with younger groups. This increased time is due to multisystem injuries, rather than the extent of maxillofacial fracture. Periodontal disease, bone resorption, and dental restorations or missing teeth are much more frequent in the geriatric age group. Rigid internal miniplate fixation eliminates some of the problems of intermaxillary wire fixation, resulting in fewer complications—that is, less risk to crown or bridge work, less weight loss, and decreased breathing problems.

The timing and staging of craniofacial fractures repair have traditionally been weighed against other possible life-threatening conditions. The early repair of facial fractures does not appear to affect adversely the recovery or outcome in patients with head injuries, however.

Much attention has recently been focused on rigid fixation (miniplates) as a method of improving fracture healing. It has been shown that fixation by means of interfragmental stabilization and compression tends to neutralize torsional and sheer forces, allowing primary bone healing and union. Rigid fixation is therefore indicated in cases where onlay bone grafts may be exposed to motion, shear, and torsional forces.

Recent contributions clearly substantiate the basic principles of maxillofacial treatment: accurate diagnosis, early anatomic fracture reduction, stable osseous fixation, and the restoration of preinjury occlusion. The care of older patients will continue to be challenging.

ROBERT A. HARDESTY, MD
Loma Linda, California

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Feeding Children Who Have Cleft Lip or Palate

SURGEONS HAVE ASSUMED that special feeding precautions should be adopted for children born with a cleft lip or palate or after the repair of these anomalies. Mothers in developing nations, however, consistently prove that immediate breast-feeding is safe.

Plastic surgeons should consider advising the use of the breast or conventional bottle and nipple combinations. Most children with clefts, even those with enormous tissue gaps, will do well at breast or bottle. Only a few will require special attention or special devices. Those few will require intensive and continuing attention because nutritional deficits impair future learning capacity.

What about feeding policy immediately after surgical repair? Comparative studies show no greater rate of complication if an infant is returned immediately to mother's breasts after lip repair. There is no evidence that a short, soft nipple or a carefully directed tip of a spoon will cause palatal dehiscence.

Perhaps the greatest mechanical hazard after a lip or palate procedure, especially the latter, is a child's finger directed into the mouth. Elbow restraints are therefore critical for a week after lip repair and two weeks after palatal repair.

JACK C. FISHER, MD
San Diego, California

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University of California, Irvine

Scott R. Miller was listed inadvertently as the medical student representative for the January Pathology Epitomes; that student was William Isenberg, PhD, of the University of California, San Francisco.

Alerts, Notices, and Case Reports

Verapamil Overdose

BRUCE W. SPURLOCK, MD
Sacramento, California

NZEERA A. VIRANI, MD
Washington, DC

CAROL A. HENRY, RN
Santa Clara, California

CALCIUM CHANNEL BLOCKERS are now among the most commonly prescribed agents for patients with cardiovascular disease. The oldest member of the class, verapamil hydrochloride, is frequently used to treat hypertension, angina, and supraventricular tachyarrhythmias. Verapamil has recently been used to prevent migraine headaches and to treat a variety of noncardiac diseases. Because of this widespread use, toxicity from overdose might be anticipated. The English-language biomedical literature contains 23 reports of cases of acute verapamil overdose in which treatment was rendered.[1-20] Only two deaths occurred in treated cases, and few long-term sequelae have been seen. We report a case of acute verapamil overdose with some unusual features. We also discuss the current understanding of the pathophysiology and treatment of this condition.

Report of a Case

The patient, a 38-year-old woman, was seen in the emergency department an hour after ingesting 60 80-mg (total, 4.8 grams) verapamil hydrochloride tablets. She was alert and oriented but said she felt lightheaded and disassociated. She had a history of migraine headaches and iron deficiency anemia. Sinus bradycardia was present at 45 beats per minute with a blood pressure of 58/30 mm of mercury. Administering ipecac led to an immediate emesis which contained no pill fragments. Calcium gluconate, 985 mg, was given intravenously as one ampule; the heart rate immediately increased to 88 beats per minute, but her blood pressure did not change. A physical examination otherwise revealed no abnormalities.

Laboratory test results were as follows: serum sodium, 132 mmol per liter (milliequivalents per liter); serum potassium, 3.1 mmol per liter; plasma total carbon dioxide, 15 mmol per liter; serum creatinine, 115 μmol per liter (1.3 mg per dl); serum calcium, 2.12 mmol per liter (8.5 mg per dl); and hematocrit, 0.29 (29%). Arterial blood gas results with the patient breathing 5 liters of oxygen by nasal cannula were P_{O_2} 149 mm of mercury, P_{CO_2} 24 mm of mercury, and pH 7.42. The electrocardiogram showed sinus bradycardia at a rate of 60 per minute and nonspecific ST segment and T-wave abnormalities. A chest x-ray film was normal. A serum toxicology screen disclosed less than 0.2 μg per ml of butalbital and no ethanol. The patient was transferred to the intensive care unit. Verapamil and norverapamil concentrations in a blood specimen drawn on admission were later reported as 1,205 μg per liter (therapeutic range, 100 to 600 μg per liter) and 915 μg per liter (no therapeutic range determined), respectively.

On the patient's arrival to the intensive care unit, a dopamine hydrochloride infusion was started and increased in a 20-minute period to 20 μg per kg per minute with only a slight increase in blood pressure to 72/31 mm of mercury. Hydration with Ringer's lactate solution was begun with a total volume of 7.5 liters given during a 2½-hour period with no resultant rise in blood pressure. The central venous pressure at the conclusion of volume resuscitation measured 13 mm of mercury. An additional 985 mg of calcium gluconate was then given intravenously without hemodynamic change. The patient had three episodes of emesis during the 2½ hours, which led to acute decreases in both heart rate and blood pressure with near syncope and finally a generalized seizure; an endotracheal tube was then inserted without assisted ventilation for airway protection. Oxygen saturation was greater than 95%, as measured by pulse oximeter. Two hours after intubation, approximately 4½ hours after ingestion, the blood pressure spontaneously rose to 120/44 mm of mercury (mean arterial pressure, 65 mm of mercury) during a 30-minute interval. The dopamine infusion dose was lowered during this time to 3 μg per kg per minute. The patient then had crushing substernal chest pain without electrocardiographic evidence of myocardial ischemia, and intravenous nitroglycerin therapy was started for the prophylaxis of occult coronary artery disease. No hemodynamic changes were seen. The patient's urine output increased from 50 to 300 ml per hour at this point. Five hours after resuscitation began, the oxygen saturation and P_{O_2} began to drop, necessitating an increase in inspired oxygen to 70%. The P_{O_2} was 57 mm of mercury, P_{CO_2} 29 mm of mercury, and pH 7.33. A pulmonary artery catheter was placed, yielding a cardiac output of 8.6 liters per minute, a calculated systemic vascular resistance of 548 dynes·sec·cm^5, a central venous pressure of 13 mm of mercury, and a pulmonary artery wedge pressure of 14 mm of mercury. A chest x-ray film (Figure 1) then showed a perihilar alveolar infiltrate. The P_{O_2} increased gradually during the next 16 hours without further treatment, and the patient was extubated. Arterial blood gas measurements with the patient breathing room air showed a P_{O_2} of 72 mm of mercury, P_{CO_2} 34 mm of mercury, and pH 7.40. Plasma glucose and serum creatinine and electrolyte levels became normal; the total creatine kinase level and MB fractions were not elevated, and the electrocardiogram remained unchanged. The patient was discharged 48 hours after admission.

Discussion

Verapamil blocks the slow, inward flux of calcium in myocardial and vascular smooth muscle and prevents the release of calcium from the sarcoplasmic reticulum. Verapamil also decreases the rate of recovery of the slow calcium channels in the sinus and atrioventricular (AV) nodes. These actions result in arteriolar smooth muscle relaxation and vasodilation (primarily in the arteriolar beds), decreased si-

(Spurlock BW, Virani NA, Henry CA: Verapamil overdose. West J Med 1991 Feb; 154:208-211)

From the Departments of Internal Medicine (Drs Spurlock and Virani) and Hospital Nursing (Ms Henry), Kaiser Permanente Medical Center, Santa Clara, California. Dr Virani is currently with the Department of Internal Medicine, Walter Reed Army Medical Center, Washington, DC.

Reprint requests to Bruce W. Spurlock, MD, Department of Internal Medicine, Kaiser Permanente Medical Center, 2025 Morse Ave, Sacramento, CA 95825.

Figure 1.—An anteroposterior chest x-ray film shows a perihilar alveolar infiltrate.

nus rate, slowed AV conduction, and negative inotropism.

Verapamil is well absorbed orally (90%) but has substantial first-pass metabolism with only 20% to 35% bioavailability. Peak concentrations occur one to two hours after oral ingestion. It is strongly bound (90%) to plasma proteins. In healthy volunteers, the half-life of verapamil varies from 2.7 to 8.2 hours with a single dose. In volunteers taking multiple doses, the half-life is increased to 4 to 12 hours. In patients with liver failure, the half-life is 14 to 16 hours. The main metabolite, norverapamil, has approximately 20% the activity of the parent compound and roughly similar pharmacokinetic properties. The drug is primarily excreted as metabolites in the urine (70%) and in feces (15%).[21]

Clinical Features

Clinical features common to most cases of verapamil overdose include cardiac conduction abnormalities, hypotension, an altered mental state, hyperglycemia, and metabolic acidosis. Two patients had seizures and respiratory arrest.[3,4] The currently understood pathophysiology of each of these aspects is discussed here.

Cardiac conduction abnormalities were present in all 23 cases reported, with bradycardia the most common finding. Atrioventricular dissociation* and junctional[2-4,7,9,12,15,17,18,20] and idioventricular[3,8,13] rhythms were the indications for ventricular pacing. First- and second-degree AV block,[7,16,18] Wenckebach phenomenon,[11,16] bundle branch block,[5,11,12] intraventricular conduction delay,[7,15] and asystole[9] have also been reported. P-wave morphology can also be altered.[7,10-12] These abnormalities may persist as long as 36 hours after ingestion even after the patient becomes clinically stable. Conduction disturbances are a result of an extended direct effect of the drug.

Hypotension is noted in almost all patients. In some patients, the blood pressure was unobtainable.[8,9,16,20] The cause of hypotension has not been clearly elucidated. Goenen and co-workers showed a diminished cardiac index with elevated central venous and pulmonary artery wedge pressures in a 16-year-old girl who ingested 8 grams, suggesting direct cardiac suppression.[1] Whether negative chronotropism or inotropism predominates is not clear. No other cases with invasive hemodynamic monitoring have been reported. An increased heart rate has been correlated with improved blood pressure in some, but not all, patients. Decreased peripheral resistance has not been reported, yet severe vasodilation is also an extended pharmacologic effect of the drug. In animals, administering dopamine and β-sympathomimetic agents further lowered the peripheral vascular resistance in experimental verapamil toxicity.[22] Hypotension also seems to be the abnormality most resistant to the various therapies. The time course to the correction of hypotension ranges from minutes to almost 24 hours and is not correlated with the amount ingested ($r = .009$).

An altered mental state usually involves confusion, although most patients are alert. Coma has also been described.[3,4,7] The mechanism is thought to be a result of cerebral hypoperfusion, but direct toxic effects must also be considered. Govoni and associates have shown direct neuronal binding with calcium channel blockers and altered neurotransmitter release.[23] The only long-term sequelae reported from verapamil overdose are cerebral anoxic damage in one patient[7] and persistent mild hemiparesis in another.[20]

Hyperglycemia is a common clinical feature of verapamil ingestion. Several in vitro and in vivo studies show β-cell calcium flux to be altered by calcium antagonists; insulin release probably behaves similarly.[13,24] Insulin infusions have been used,[13,19] but glucose levels return to normal within 24 hours in most patients without treatment. Metabolic acidosis is a result of increased lactate production from hypoperfusion.[13] The condition is usually not severe ($pH > 7.10$) and corrects as the patient becomes hemodynamically stable. Hyperkalemia was reported in one patient,[19] whereas hypokalemia occurred in another.[18]

Therapeutic Approaches

The general practice of managing any case of overdose involves enhancing elimination, preventing further absorption, and administering an antidote if available. In cases of verapamil overdose, charcoal and a cathartic agent should be used. Verapamil cannot be dialyzed.

Most reports in the literature have concentrated on the hemodynamic aspects of treatment. Various therapeutic regimens have been used with different degrees of success (Table 1). The administration of calcium salts is the most widely used therapy but with tremendous disparity in results. In early reports of verapamil overdose, only calcium injections were used, with complete hemodynamic response. Recent cases indicate a marked resistance to these agents, however.[1,3,5,7,8,13] Midtbø and Hals studied the use of calcium infusions in patients taking therapeutic doses of verapamil for essential hypertension and found no change in mean heart rate or blood pressure.[25] The mechanism by which extracellular calcium might aid in the treatment of verapamil toxicity has not been delineated. No reports of death or clinical deterioration associated with calcium administration have been published, but some authors question the use of calcium in critically ill patients with normal calcium levels.[26,27]

The most controversial area of treatment is the use of sympathomimetic amines. Isoproterenol hydrochloride has been recommended as initial therapy for patients with bradycardia or hypotension. Its direct inotropic and chronotropic effects may be useful. The peripheral vasodilation that accompanies its use may be deleterious, as mentioned earlier.

*References 1, 3, 5, 6, 9-12, 14, 16-18, 20.

In two patients the use of epinephrine was successful, suggesting that combined α- and β-adrenergic activity might avoid vasodilation. In one patient, however, administering metaraminol bitartrate had negligible effects. Dopamine has also been used frequently, usually in the range of 15 to 30 μg per kg per minute, which is considered to be an α-vasoconstrictive dose. The use of dopamine only has seldom been effective. Several reasons are possible for the lack of effectiveness of α-adrenergic drugs. There may be direct resistance to the agent because of altered α receptors. The associated metabolic alterations with acidosis and hyperglycemia may prevent a clinical response. Finally, β-adrenergic increases in inotropy or chronotropy may be required because of direct cardiac suppression by verapamil. In one patient, amrinone lactate was more effective in combination with isoproterenol than isoproterenol alone.[1] The improvement was postulated to be a result of different mechanisms of action. Amrinone inhibits phosphodiesterase III, producing increased levels of cyclic adenosine monophosphate, which may alter calcium flux or bind to calmodulin; thus, inotropy is potentially increased. The use of neither norepinephrine bitartrate nor dobutamine hydrochloride has been shown to be effective alone or in combination with other vasoactive agents.

Atropine sulfate was used in eight patients, occasionally associated with increases in heart rate but never with changes in blood pressure. In animals, the use of atropine had no effect on survival.[22] Ventricular pacing was usually instituted when heart rate and blood pressure remained low after trials of atropine and isoproterenol. In only one patient did ventricular pacing stabilize the blood pressure. Despite the frequency of acidosis in verapamil overdose, sodium bicarbonate has seldom been used.

Unusual Features of This Case

The case reported here demonstrates several interesting points. Calcium gluconate was clearly not effective in altering the patient's overall clinical course, causing only a slight increase in her heart rate soon after administration and no effect on her blood pressure. The dose may have been too small or its administration not frequent enough, or some other factor limited its usefulness. Giving dopamine alone had little effect even at a vasoconstrictive dose. Likewise, massive volume expansion did not improve the patient's blood pressure in the presence of pronounced vasodilation. Most notable, though, is the improvement in blood pressure two hours after the last therapeutic maneuver. The improvement that occurred in our patient's condition raises concerns about causality in the therapeutic regimens of previous reports. The only direct evidence of effectiveness of any therapy is found in animal models. Strubelt has shown that adrenergic agents did keep rats alive significantly longer than did placebo, and their use was associated with increased cardiac output.[22] Once our patient became hemodynamically stable, she had a high cardiac output and low systemic vascular resistance. Unfortunately, these values were not obtained before stabilization. The low systemic vascular resistance from verapamil overdose would argue against the use of drugs such as isoproterenol that would cause further vasodilation.

Episodes of hypoxemia without an adequate explanation have been reported only twice before. In our patient pulmonary edema developed with normal pulmonary artery wedge and central venous pressures and an elevated cardiac output. The cause of the hypoxemia is unclear, but several mechanisms can be postulated. Pulmonary capillary hydrostatic pressures may have been transiently elevated before the pulmonary artery catheter was placed. This mechanism would parallel one etiologic model for neurogenic pulmonary edema.[28] The near-syncopal episode and seizure in our patient as a result of increased vagal tone from emesis may have been the neurogenic stimulus. The rapid resolution of severe hypoxemia is consistent with the clinical course of neurogenic pulmonary edema. Alternatively, the metabolites of verapamil, generally thought to be clinically irrelevant, could be responsible for a direct membrane permeability defect. The time course until pulmonary edema developed in our patient correlates with the production of verapamil me-

TABLE 1.—*Types of Therapy for Verapamil Overdose in Reported Cases*

Therapy	*Patients, No.*	*Dose*	*Reference Source*
Calcium gluconate	11	1 to 6.6 grams, 2 continuous infusions	1,2,5-11,14,15
Calcium chloride	4	1 to 2.0 grams, 1 continuous infusion	4,13,17,18
Calcium	1	No dose given	3
Dopamine hydrochloride	11	15 to 30 μg/kg/min	1,4-7,9,13,17,18
Isoproterenol	11	1 to 4 μg/kg/min	1,3-9,13,17,20
Ventricular pacing	8	N/A	3,6,8,9,12,13,17
Atropine sulfate	9	0.5 to 2.0 mg	6-8,12-14,17,19,20
Intravenous fluids	9	Total volume not given	3,4,11,13,16-20
Epinephrine	2	0.8 μg/kg/min, no dose	5,8
Sodium bicarbonate	3	No dose given	3,14,19
Norepinephrine	3	2 to 4 μg/min in one case; no dose given in others	3,8,18
Metaraminol bitartrate	1	5 mg	10
Amrinone lactate	1	1 mg/kg load, 6 μg/kg/min	1
Glucagon	1	10 mg	7
Prenalterol hydrochloride	1	10 mg	7
Dobutamine hydrochloride	1	40 μg/kg/min	7
Furosemide	1	2 mg/min	7
Dexamethasone	1	25 mg	11
Methscopolamine bromide	1	No dose given	16

N/A = not applicable

tabolites. A pulmonary vascular permeability defect would have to be transient and easily repaired to explain the 16-hour time course of resolution. This pulmonary edema was apparently not cardiogenic.

While emesis is usually effective in removing undigested pills in patients who have overdosed, the use of ipecac in a patient with hypotension is dangerous. The yield is frequently poor, and vagally induced decreases in heart rate in hemodynamically unstable patients should discourage its use. The increased vagal tone witnessed in our patient probably exacerbated the hypotension and led to her generalized seizure. Gastric lavage is as effective and safer in these patients.

The search for an antidote for verapamil overdose is, to date, incomplete. A drug that reverses nondepolarizing neuromuscular blockade, 4-aminopyridine, has been used effectively in cats.[29] In an extensive study, Korstanje and colleagues examined the calcium-entry promoters Bay k 8644 and CGP 28932, as well as 4-aminopyridine, and found them all to be effective in rabbits.[30] Bay k 8644 was substantially better at improving the hypotension and electrocardiographic and heart rate abnormalities. No human trials of any of these agents have been reported.

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Phlegmasia Cerulea Dolens Associated With the Lupus Anticoagulant

BRUCE A. BAETHGE, MD
D. KEITH PAYNE, MD
Shreveport, Louisiana

PHLEGMASIA CERULEA DOLENS (PCD) is a severe form of peripheral venous thrombosis characterized by massive edema, severe pain, and cyanosis. It is the result of the complete obstruction of the venous drainage of a limb and may result in shock, distal gangrene, pulmonary embolus, or death.[1] Phlegmasia cerulea dolens often occurs in association with hypercoagulable states including clotting disorders,[2] malignancy,[3] oral contraceptive use,[4] trauma,[5] and the postsurgical and postpartum periods.[1] In the following report, we describe the occurrence of PCD in a woman who was found to have the lupus anticoagulant. A computerized literature search elicited no previous reports of this association.

Report of a Case

The patient, a 50-year-old woman, was admitted to the hospital because of sudden pain and swelling of the right calf and thigh. She had suffered an episode of deep vein thrombosis in the same leg three years previously. Long-term warfarin sodium (Coumadin) therapy had been discontinued two weeks before her symptoms started. She said she had not had recent trauma or prolonged periods of immobility. There was no history of a clotting disorder or systemic rheumatic disease.

On physical examination the patient was morbidly obese and had marked edema of the right leg, which had a dusky, erythematous appearance. There was a difference in circumference of 8 cm at midthigh and 6 cm at midcalf of the right leg compared with the left. Dorsalis pedis and posterior tibial pulses were palpable in the right foot on initial examination.

Admission laboratory tests revealed a serum creatinine level of 194.5 μmol per liter (2.2 mg per dl) and a blood urea nitrogen concentration of 8.6 mmol per liter of urea (24 mg per dl). A urinalysis revealed no proteinuria. The prothrombin time was 14 seconds with a normal control range of 10 to

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From the Sections of Rheumatology (Dr Baethge) and Pulmonary Disease (Dr Payne), Department of Medicine, Louisiana State University Medical Center, Shreveport.

Reprint requests to Bruce A. Baethge, MD, LSU Medical Center, PO Box 33932, Shreveport, LA 71130-3932.

ABBREVIATIONS USED IN TEXT

APTT = activated partial thromboplastin time
PCD = phlegmasia cerulea dolens

13 seconds. The activated partial thromboplastin time (APTT) was 57 seconds with a normal control range of 22 to 31 seconds using activated cephaloplastin as the thromboplastin reagent (Baxter/Dade, Rutherford, New Jersey). The APTT corrected to only 41 seconds after a 1:1 mix with normal serum, confirming the presence of an inhibitor. A thromboplastin dilution assay was consistent with the presence of the lupus anticoagulant (Table 1). She also had a positive rapid plasma reagin test with a nonreactive microhemagglutination assay for *Treponema pallidum*. Antithrombin III levels were within the normal range.

The diagnosis of phlegmasia cerulea dolens was made on clinical grounds, and intravenous heparin therapy was started. There was no evidence to support the diagnosis of systemic lupus erythematosus. Impedance plethysmography was attempted but was technically impossible because of the size of the right leg (Figure 1). Venography was not done because of the concern that her azotemia would be exacerbated. Ultrasonography and computed tomography of the pelvis and right leg revealed massive edema with enlarged subcutaneous veins consistent with occlusion of the deep venous system. No evidence of a mass lesion or extrinsic compression of the venous system was seen.

Despite leg elevation and continuous heparin therapy (500 units per hour) for 36 hours, swelling and cyanosis continued and the patient suffered intense pain. The distal pulses could no longer be palpated in the right foot and were detectable only by Doppler. Streptokinase therapy was initiated with an intravenous bolus of 250,000 units and maintained at a continuous infusion of 100,000 units per hour for three days. The patient had a notable reduction in pain and swelling. Following the discontinuation of streptokinase, heparin therapy was resumed. Over the next 14 days, there was a gradual improvement in the appearance of the leg with less swelling and the return of palpable pedal pulsations. A year after discharge, the patient remains on continuous warfarin therapy with venous stasis dermatopathy and persistent edema of the right lower extremity.

Discussion

The lupus anticoagulant is an acquired inhibitor of blood coagulation initially described more than 30 years ago in patients with systemic lupus erythematosus.[6] The term "lupus anticoagulant" is a misnomer because bleeding rarely occurs without the presence of additional clotting abnormalities, and clinically the lupus anticoagulant is associated with thrombotic events.[7-9] The lupus anticoagulant occurs in as many as 16% of patients with systemic lupus but can also be found in association with other autoimmune disorders, with the use of certain drugs, and in patients with no underlying problems.[7-9]

Lupus anticoagulant activity has been shown to be the result of immunoglobulin G and immunoglobulin M antibodies directed against phospholipids including cardiolipins.[10] It is not known how the lupus anticoagulant leads to thrombosis. Suggested hypotheses include its interacting with endothelial or platelet cell surfaces (or both) that directly results in increased platelet aggregation, or modulation of the protein C pathway by the lupus anticoagulant that leads to inhibition of the fibrinolytic system and thus indirectly results in clot formation.[11] Anticoagulation therapy is usually successful in the treatment of venous thrombosis associated with the lupus anticoagulant.[7,8]

The lupus anticoagulant is recognized by a prolongation of the APTT that occurs in all patients and by prolongation of the prothrombin and thrombin times that is found in some patients.[8] Mixing studies will confirm the presence of a circulating inhibitor that does not correct with the addition of normal plasma. The dilute tissue thromboplastin assay or a platelet neutralization procedure can be used to confirm the presence of the lupus anticoagulant.[10,12] Additional laboratory features found in some patients include the presence of a biologically false-positive test for syphilis and thrombocytopenia. The association of the lupus anticoagulant with arterial and venous thrombosis, spontaneous abortion, and other clinical abnormalities has recently been the subject of exten-

TABLE 1.—*Thromboplastin Dilution Assay**

Dilution	Prothrombin Time: Patient, s	Prothrombin Time: Normal Control, s	Ratio†
1:1	14	14	...
1:100	82.4	45.9	1.8
1:1,000	170.7	91.6	1.9

*Thromboplastin C, Baxter/Dade, Becton Dickinson & Company, Rutherford, NJ 07070.
†Ratio is of the patient/control prothrombin times using diluted Thromboplastin C. In our laboratory the lupus anticoagulant is considered present when the ratio at the 1:100 dilution is greater than 1:1.5 and when the ratio at the 1:1,000 dilution is greater than 1.1.7.

Figure 1.—The photograph shows the pronounced edema and dusky appearance of the right leg in a patient with phlegmasia cerulea dolens.

sive investigation and has been called the anticardiolipin syndrome.[13]

Phlegmasia cerulea dolens is a life-threatening disorder that requires aggressive intervention to combat the high frequency of morbidity and mortality.[1,14,15] The treatment of PCD includes anticoagulation, thrombolytic therapy, and surgical thrombectomy used alone or in combination.[14,15] A recent review of the therapeutic options for PCD suggests that surgical intervention is needed when patients fail to respond to heparin therapy within 6 to 12 hours.[15] The discovery of the lupus anticoagulant in our patient led to the institution of thrombolytic therapy that proved to be successful.

It has been suggested that all patients with hypercoagulable clotting abnormalities are at high risk for the development of PCD.[2] This case supports that suggestion. Cohen and colleagues have recently described six cases of PCD in patients who had associated hypercoagulable states, including heparin-induced thrombocytopenia, congenital protein C deficiency, and antithrombin III deficiency.[2] The authors commented that recognition of an underlying coagulopathy is essential for the proper management of PCD. We agree and think the lupus anticoagulant should be included as another coagulopathy associated with PCD.

Our patient had no evidence of an underlying collagen vascular disease or occult malignant neoplasm. The lupus anticoagulant contributed to the development of PCD, although she had morbid obesity and a previous deep vein thrombosis as additional risk factors. She will require anticoagulation therapy indefinitely.

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Rhabdomyolysis Associated With Lovastatin and Erythromycin Use

DAVID H. SPACH, MD
J. ERIC BAUWENS, MD
CHRISTINE D. CLARK, MD
WYLIE G. BURKE, MD, PhD
Seattle, Washington

LOVASTATIN, a hydroxymethylglutaryl-coenzyme A reductase inhibitor used to treat patients with hypercholesterolemia, has become a commonly administered drug. Its use has been associated with a low incidence of side effects that include elevated aminotransferase levels, skin rash, gastrointestinal symptoms, and skeletal muscle abnormalities.[1,2] Clinically, the most important of these side effects is the skeletal muscle abnormalities that can manifest as asymptomatic creatine kinase elevations; muscle aches, tenderness, and weakness; and rhabdomyolysis.[2] Patients at greatest risk of muscle abnormalities developing include those with an underlying illness or concurrently taking medication such as cyclosporine, gemfibrozil, or niacin.[1,2] We present a case of rhabdomyolysis associated with lovastatin use that occurred shortly after a course of erythromycin. In addition, we review two previously reported cases of rhabdomyolysis that occurred after the concomitant use of lovastatin and erythromycin and conclude that erythromycin should be added to the known list of drugs associated with lovastatin-induced rhabdomyolysis.

(Spach DH, Bauwens JE, Clark CD, Burke WG: Rhabdomyolysis associated with lovastatin and erythromycin use. West J Med 1991 Feb; 154:213-215)

From the Departments of Internal Medicine (Drs Spach, Bauwens, and Burke) and Pathology (Dr Clark), University of Washington School of Medicine, Seattle.

Reprint requests to David H. Spach, MD, Harborview Medical Center, ZA-89, 325 9th Ave, Seattle, WA 98104.

Report of a Case

The patient, a 68-year-old woman with diabetes mellitus, coronary artery disease, congestive heart failure, and chronic renal insufficiency, was admitted to the hospital for the evaluation of dyspnea and pulmonary infiltrates. Seven months before admission, a regimen of lovastatin, 20 mg twice a day, was started for hypercholesterolemia. The patient's baseline total cholesterol level of 7.34 mmol per liter (282 mg per dl) decreased to 4.45 mmol per liter (171 mg per dl) after six months of lovastatin therapy. Nine days before the current admission, the patient had been admitted to the hospital with dyspnea, fever, and pulmonary infiltrates. During this previous hospital admission, she received a combination drug containing ampicillin sodium and sulbactam sodium intravenously for three days, followed by a combination of amoxicillin and clavulanate potassium orally for three days. She responded well and was discharged on the oral antibiotic regimen but was readmitted to the hospital four days later with a recurrence of her symptoms. Her medications on admission included lovastatin, 20 mg twice a day; amoxicillin-clavulanate; furosemide; sucralfate; ranitidine; allopurinol; insulin; isosorbide dinitrate; enalapril; and digoxin.

Pertinent physical examination findings included rales at the bases of both lung fields, a holosystolic murmur heard best at the mitral region, and an absence of hepatosplenomegaly. Laboratory studies on admission elicited the follow-

ing values: serum potassium, 4.2 mmol per liter; serum creatinine, 309.1 μmol per liter (3.5 mg per dl); serum creatine kinase, 35 U per liter; and total bilirubin, 8.6 μmol per liter (0.5 mg per dl). While the patient was breathing room air, a specimen of arterial blood showed that the pH was 7.45, the Pa_{O_2} was 7.1 kPa (53 mm of mercury), and the Pa_{CO_2} was 4.4 kPa (33 mm of mercury). An echocardiogram was obtained two days after admission and revealed severe mitral regurgitation, mild aortic regurgitation, and moderately decreased left ventricular function.

Three days after admission, the amoxicillin-clavulanate therapy was changed to erythromycin. On the seventh day after admission, the patient underwent a bronchoscopic examination, and tests were negative for acid-fast bacilli, bacteria, and legionella direct fluorescent antibody. Biopsy findings were consistent with idiopathic pulmonary fibrosis, and a course of prednisone, 60 mg a day, was started. About 24 hours after receiving her first dose of prednisone, the patient's dyspnea decreased, and over the following 72 hours the pulmonary infiltrates present on chest radiograph resolved considerably.

Five days after completing the ten-day course of erythromycin, the patient complained of muscle weakness and tenderness. At this time, her pulmonary and cardiac states were stable and jaundice had not developed. The following day her urine turned dark, and laboratory studies revealed a serum creatine kinase level of 26,400 U per liter, serum aldolase 243.2 U per liter, serum potassium 6.6 mmol per liter, and serum phosphate 2.3 mmol per liter (7.1 mg per dl). The patient received vigorous alkaline fluid and diuretic therapy; the lovastatin therapy was discontinued. Her urine output became fixed at 10 ml per hour, and her serum creatinine level of 309.1 μmol per liter (3.5 mg per dl) increased to 371.3 μmol per liter (4.2 mg per dl). Dialysis was recommended but was refused by the patient in repeated discussions throughout this period. She died two days later of progressive renal failure and pulmonary edema.

Additional laboratory tests revealed normal thyroid function and a lovastatin concentration of 48 ng equivalents per milliliter. The lovastatin concentration, from a specimen drawn 2½ hours after the patient's last dose, represents an almost threefold elevation above the expected value derived from pharmacokinetic studies (J.A. Tobert, MD, PhD, written communication, March 1989). At autopsy, both quadriceps muscle specimens showed edema and necrosis of individual muscle fibers in a patchy distribution; occasional macrophages and rare lymphocytes were seen. There were no regenerating fibers (Figure 1).

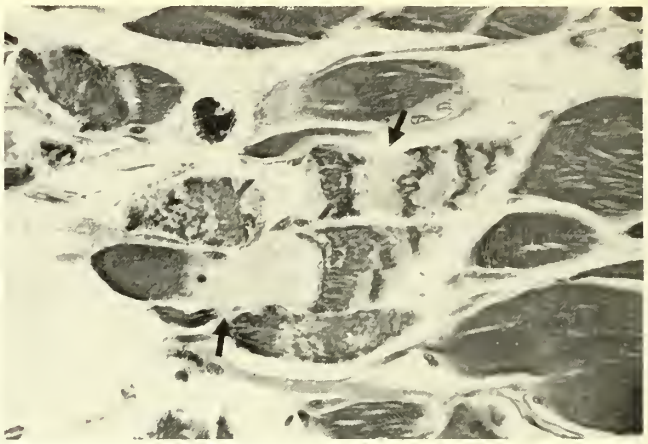

Figure 1.—The biopsy specimen of the right quadriceps muscle shows patchy myocyte necrosis (**arrows**); no significant inflammation is present (trichrome, original magnification × 400).

Discussion

We report the third case of lovastatin-associated rhabdomyolysis occurring after the completion of a course of erythromycin. Several pieces of information lead us to conclude that lovastatin was the specific etiologic agent causing this patient's rhabdomyolysis: there was no evidence of any other known cause of rhabdomyolysis, the patient's serum lovastatin level was elevated nearly threefold above the expected level, and postmortem quadriceps muscle biopsy findings were consistent with a toxic injury or drug-induced rhabdomyolysis.

The muscle biopsy in this case was most useful for excluding polymyositis which, if present, should have revealed regenerating muscle fibers or an interstitial inflammatory infiltrate. In addition, no direct evidence of an infectious cause was seen. Degenerative changes on a muscle biopsy specimen similar to those seen in our patient can occur with an acquired myopathy associated with hyperthyroidism, but the results of thyroid function tests were normal in our patient. Three previous muscle biopsy reports from patients with lovastatin-associated rhabdomyolysis were limited but noted cell necrosis without inflammation,[3] nonspecific abnormalities without inflammation or necrosis,[4] and type II atrophy with scattered muscle fiber degeneration.[5]

The efficacy and adverse effects of lovastatin use have recently been reviewed.[2] Cases of myopathy were reported in 17 patients, with myopathy being defined as a combination of muscle pain or weakness plus a tenfold or greater elevation in creatine kinase values.[2] Plasma levels of lovastatin were measured in 6 of the 17 patients, and all were elevated severalfold or more. Patients particularly at risk of having muscle injury were those concomitantly taking cyclosporine, niacin, or gemfibrozil. In this series, all patients recovered after discontinuing lovastatin use, including two patients with rhabdomyolysis-induced renal failure. The patient we present is the second patient to require hemodialysis,[3] and had she not refused hemodialysis, she may have recovered from the acute episode of lovastatin-associated rhabdomyolysis.

In a recent report of a patient taking lovastatin, rhabdomyolysis was noted to develop shortly after the patient completed a 13-day course of erythromycin.[6] The patient, a 65-year-old man with coronary artery disease and chronic renal failure, received erythromycin for the treatment of pneumonia. At the end of the antibiotic course, weakness, myalgias, and a pronounced elevation in the creatine kinase level developed, similar to the findings in our patient. An additional reported case of rhabdomyolysis may have been associated with concurrent lovastatin and erythromycin use.[7] This occurred in a 46-year-old man with a heart transplant who took prednisone, cyclosporine, and lovastatin for more than a year, without any muscle abnormalities. Acute rhabdomyolysis developed shortly after he completed a course of erythromycin. Rhabdomyolysis in this case was attributed to the combination of cyclosporine and lovastatin. Because of his previous stable course, we suspect that erythromycin may have triggered the episode of rhabdomyolysis.

For several reasons, we strongly suspect that erythromycin use contributed to our patient's lovastatin-associated

rhabdomyolysis. Before receiving the course of erythromycin, our patient had taken lovastatin for more than six months without any muscle difficulties. Prednisone therapy, which was started shortly after the erythromycin, could possibly have played a role in the rhabdomyolysis, but it has not been previously associated with lovastatin-induced rhabdomyolysis. Our patient's course of rhabdomyolysis was similar to that of the other two cases described involving erythromycin. Specifically, in all three cases the rhabdomyolysis occurred after the course of erythromycin was completed. The mechanism of the lovastatin-erythromycin interaction is unknown, but it has been proposed that erythromycin inactivation of hepatic microsomes alters the metabolism and excretion of lovastatin. An alternative explanation involves erythromycin displacing protein-bound lovastatin.[6] We therefore speculate that initiating erythromycin therapy increases lovastatin concentrations, muscle injury begins on a low-grade level, and clinical symptoms and signs of overt rhabdomyolysis develop at a later point.

The apparent association of erythromycin and lovastatin use with rhabdomyolysis is an important one. As the use of lovastatin continues to rise, the chance of its concomitant use with erythromycin, which is frequently prescribed for respiratory tract and skin infections, will certainly increase. We therefore recommend caution when simultaneously administering lovastatin and erythromycin. In addition, physicians should consider temporarily discontinuing lovastatin during periods of acute illness because of the potential for alterations in drug metabolism, the increased susceptibility to drug toxicity, and the frequent use of multiple medications that may interact adversely.

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Commentary

Can a Clinician Be a Scientist?

WILLIAM P. LONGMIRE, Jr, MD, *Los Angeles, California*

Presented at the 1990 Annual Scientific Session of the California Medical Association in March 1990, Anaheim, California.

We might define a scientist as one concerned with establishing new facts, principles, or methods by experiments. And we might define a clinician as an expert in or practitioner of clinical medicine, one who attempts to improve the well-being of patients. The question then is, can a practitioner of clinical medicine ever also be a specialist in a branch of knowledge concerned with establishing new facts, principles, or methods by experiments?

During the first century and a half of this country's existence, what passed as basic science teaching in most of our schools was done exclusively by faculty holding the MD degree. They were practicing physicians who made some effort, often not very great, to have additional or special knowledge in a particular science such as anatomy, physiology, and materia medica. There were no true basic scientists in most of our schools. This system of proprietary medical school education, which undoubtedly served a good purpose at one stage in the development of this country, was abused and grossly outmoded when it was finally forced out of existence during the second decade of the 1900s by the release of the Flexner Report.

Although few writers have given him due credit, the dramatic improvement in medical education in this country was really initiated by Dr Arthur Dean Beven, founder of the Council on Medical Education of the American Medical Association and its chair for 24 years. After several years of somewhat ineffective efforts on its own to improve American medical schools, the Council on Medical Education joined forces with Dr Henry S. Pritchett, president of the Carnegie Foundation, and Mr Abraham Flexner was selected to survey and evaluate the medical schools in this country. His findings were published as the Flexner Report of 1910. The report was labeled, "a classic of muckraking journalism," but it caught the attention of the medical profession. It also stirred the concern of the public and permitted the Council on Medical Education to close or combine 92 of the 155 schools then in existence, thereby bringing about a most remarkable improvement in the standards of medical education.

The two principles Flexner stressed in his ideal medical education were that physics, chemistry, and biology (the basic sciences) provided the intellectual foundation of modern medicine and that the scientific method applied to the practice of medicine as well as to research. It makes no difference to science, said Flexner, whether usable data be obtained from a slide beneath a microscope or from a sick man stretched out on a cot. Flexner knew that the average family doctor would never engage in research, but he insisted that the scientific method was indispensable to the everyday work of good patient care.

As a result of these efforts, started in the early part of this century, we physicians of today have all been educated in scientific medicine and use the principles of logic and assessment based on a knowledge of the fundamental sciences. We are, or should be, scientists using the scientific method in the care of each of our patients.

There is, however, another level of medical science that most of us would not be prepared to, nor wish to, attain. That is the scientist who is concerned with establishing new knowledge by observation, study, or experimentation.

Practicing physicians as medical scientists employ the scientific method using known and established facts in the care of their patients. The second level of medicine is a physician involved in establishing new knowledge that may subsequently be used in the practice of scientific medicine. It is the place of this medically trained investigator in the field of research, or in the creation of new knowledge, that is of major concern today.

Lewis Thomas, in his delightfully readable book, *The Youngest Science*, tells of the report of a Presidential committee he chaired in which three levels of medical technology were described:

- Genuine high technology, exemplified by the Salk and Sabin poliomyelitis vaccines, which simply decimated a major disease at very low cost by providing protection against three strains of poliovirus;
- "Halfway" technology applied to the management of disease when the underlying mechanism is not understood and when medicine is obliged to do whatever it can to shore things up and postpone incapacitation and death at whatever cost—usually very high cost, indeed—illustrated by open-heart surgery, coronary artery bypass, and the replacement of damaged organs by transplanting new ones;
- Nontechnology, the kind of things physicians do when there is nothing to be done, as in the care of patients with advanced cancer or senile dementia.

The committee suggested that the rising cost of health care was resulting from efforts to treat diseases of the halfway or nontechnology class, and it recommended that more basic research on these ailments be sponsored by the National Institutes of Health (NIH) so that genuine high technology might be developed to totally eliminate the major diseases.

(Longmire WP Jr: Can a clinician be a scientist? West J Med 1991 Feb; 154:216-217)

From the Division of General Surgery, Center for the Health Sciences, University of California, Los Angeles, School of Medicine. Dr Longmire is a recipient of the California Medical Association's 1990 Golden Apple Award. This award spotlights exceptional physicians who have made a lifelong commitment to teaching and are renowned for their charismatic, scientific, and educational talents.

Reprint requests to William P. Longmire, Jr, MD, Department of Surgery, Center for the Health Sciences, UCLA School of Medicine, 10833 Le Conte Ave, Los Angeles, CA 90024-1749

This report would seem to categorize medical care in three appropriate classes and to propose a future approach to the health care problem that is intellectually appealing. The summary of the report might be faulted, however, for expressing slight distaste for what were at that time, and are to a great extent today, the newest and most advanced therapies available, even if they only postpone incapacitation and death at extremely high cost.

Later in his book, Thomas, after surviving a life-threatening experience himself with exsanguinating hemorrhage from an occult vascular abnormality of the colon, conceded that he was "more than ever a believer in the usefulness of technology, the higher the better," and concluded that the body "runs itself, beyond my management, but needs repairs by experts from time to time."

One hopes that all high technology would be as easily and readily transferable to the clinic and to patient care as distributing and administering the Salk vaccine to well children. Undoubtedly, preventing all human illness is the ultimate goal, but in the meantime we cannot afford to drop all halfway technology, a great deal of which is amazingly effective, nor should we abandon efforts to improve or to develop new halfway technologies as we await the millennium of the disease-free world.

It is the development or the adaptation of the therapeutic or preventive, genuinely high technology and the development and refinement of the more immediately remedial halfway technology that are being threatened today. Dr David A. Hamburg, former president of the Institute of Medicine, has commented,

> The authentic biological revolution that has been generated by several decades of intensive basic research is not easily translated into clinically valid applications. An interpreter is needed, and it is the clinical investigator who serves that function. Clinical research remains the vital bridge between advances in basic science on the one hand and improvements in health care—diagnostic, therapeutic or preventive—on the other.[1]

The importance of the clinical investigator may not be fully appreciated even by well-informed persons. Some three decades ago, Albert Tannenbaum, then president of the American Association for Cancer Research, spoke of the importance of basic science research using as an example the problem of postoperative suppuration that plagued England more than 100 years ago. Most major surgical procedures done at that time resulted in death due to suppuration. A growing professional and public concern resulted in the formation of a British Empire suppurative campaign. Meanwhile, a Frenchman was demonstrating that fermentation was caused by living organisms that dropped from the air into wine vessels. This man, of course, was Louis Pasteur. Here, Tannenbaum overlooked a most important aspect of clinical research when he stated that Pasteur's work led to antiseptic surgery and largely to the solution to the suppuration problem. Tannenbaum omitted an essential step: It was Lister, a clinical surgeon concerned with suppuration of wounds in his patients, who applied Pasteur's basic observations of the importance of airborne organisms to clinical surgery. It was the clinician seeking the solution to a clinical problem who seized upon the observations of the basic scientist for the answer. The essential role of the clinical investigator or scientist is well illustrated in this historical anecdote.

Dr James Wyngaarden, former Director of the National Institutes of Health, has also expressed concern about this problem and how it has affected the applications for research funds to the NIH: "New MD applicants are competing less well than new PhD applicants." Wyngaarden proposes an answer for this decline in clinical investigators or scientists:

> Success for an MD investigator is increasingly dependent on substantial training with the methodologies of complex modern science. If a young physician today wishes to contribute new knowledge to medicine, he must spend time, generally speaking, 2 years, in the study of methodologies of complex medical science. Gone are the days when a 3 month or 6 month rotation in a laboratory, frequently the hospital pathology department, could qualify a young physician as an academician or a scientist.[1]

Despite the obvious need for appropriately trained physicians to transfer today's dramatic scientific advances to bedside medicine, all the evidence indicates that we are moving in the opposite direction. Dr Rudi Schmid, former dean of the School of Medicine, University of California, San Francisco, reported to the Advisory Committee to the Director of the NIH that fellowship and training support, which had composed about 10% of the total NIH research budget in 1975, had dropped to only 5% ten years later, and it now represents about 4%. During a two-year period of the mid-1960s, about 1,300 research training positions were eliminated, largely based on the belief that most clinical research trainees failed to continue in an academic or research career. A recent NIH study has verified, however, that NIH extramural research fellowship support over several decades produced researchers and teachers in 83% of trainees.

America cannot hope to maintain its eminence in scientific medicine unless means can be found to support and to develop succeeding generations of new clinical scientists who are prepared to apply the newest and latest scientific developments and technologies to the problems of clinical medicine and to assist in proving them safe and effective for general medical use.

As Wyngaarden says, to be a first-rate scientist and a well-qualified physician is a demanding calling. Those young physicians able and willing to enter into this difficult career must be encouraged and supported by every available means if we are to maintain our position in the forefront of scientific world medicine.

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Editorials

Change—Threat or Opportunity

STUDS TERKEL, writer and reporter, said recently that change is inevitable but often resisted or even opposed. Although sharing change can be a bond and relishing change can be invigorating, physicians especially resist change forced by others or required by regulations.

Physicians face accelerating pressures to change: challenging scientific discoveries, new techniques, administrative restrictions, patients' demands, new forms of competition, and more rigorous quality assurance. Fox, Mazmanian, and Putnam, in a study of 340 physicians, found that we meet change in several ways.[1] Some accommodate passively and tend to be angry and resentful as they do so. Most make incremental moves. Others find entirely new directions to explore. They transform.

What causes physicians to change? A few change because they want to excel. Many become aware of innovations and react to them gradually. Some seek new solutions stimulated by patients' difficult problems. Regardless of motivation, making modifications requires repetition of new data or circumstances. Learning and changing are not first-pass phenomena. Finally, a variety of sources of information are necessary—experts, colleagues, literature, seminars, courses, and rounds.

One element in a successful approach to change is involvement. Whether change is sparked by scientific advances or imposed by public policy, physicians who adapt are the ones who participate. They ask questions. They request consultations. They vote. They run for office. They study. They write letters to professional organizations, to editors, to political leaders and other policymakers. They make themselves heard. They convert negatives to positives, so problems become challenges. They take risks. They recognize that others are undergoing change during these troubled economic times. To borrow from Arnold Toynbee, they regard medicine as a "movement and not a condition; a voyage and not a harbor."

Physicians who cope well do so by observing, thinking, and acting. They view change as opportunity.

LINDA HAWES CLEVER, MD

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Retinal Vasculitis

DISEASES OF THE RETINAL VASCULATURE are among the most serious problems in ophthalmology. They form a heterogeneous group of disorders that includes such diverse afflictions as the chronic retinal ischemia associated with diabetic microvasculopathy and the sudden, devastating visual loss of a central retinal artery occlusion. In this issue, Rosenbaum, Robertson, and Watzke present an overview of one important, but poorly understood, category of vascular disease: retinal vasculitis.[1]

Retinal vasculitis should not be considered a single disease entity. It appears to be a nonspecific immunologic reaction of retinal arterioles or venules to various antigenic stimuli and is a finding in many different systemic and local disease states. In some patients, vasculitis results in no visual disturbance. The disorder can, however, lead to serious, sight-threatening complications, including vascular occlusion with infarction of the retina, or vascular leakage with retinal edema. Late sequelae may include retinal neovascularization leading to vitreous hemorrhage or tractional retinal detachment.

Because retinal vasculitis can be a manifestation of systemic disease, it is often evaluated and managed best by an ophthalmologist and internist working as a team, drawing on each other's special skills and experience. An organized approach to retinal vasculitis is clearly needed to ensure the best patient care.

Included in this approach should be the appropriate use of terms to facilitate communication, yet even the designation "vasculitis" has been a source of confusion. Strictly speaking, the adjectival ending "-itis" indicates inflammation, but in practical terms, many vascular disorders have been called vasculitis by ophthalmologists, whether or not they are characterized histopathologically by the presence of inflammatory cells in vessel walls. Confusion arises because the signs and complications of retinal vasculitis may be mimicked by noninflammatory disorders. Vascular sclerosis, for example, can occasionally be confused with inflammatory sheathing of vessels. Furthermore, vascular occlusion by inflammation, thrombus formation, and embolization can all result in a similar clinical picture. Although ophthalmologists have the unique opportunity to view retinal vessels through transparent media, the tissues are not available for routine biopsy and clinicopathologic correlation.

Unfortunately, various vascular disorders that are not primarily inflammatory have been called retinal vasculitis. "Benign retinal vasculitis," for example, is a unilateral condition of young adults characterized by optic nerve head swelling that can mimic central retinal vein occlusion.[2] Although an inflammatory cause is hypothesized by some,[3] abnormal clotting and fibrinolytic mechanisms are thought to be the underlying cause by others.[2,4] Use of the term "vasculitis" for the ocular disease associated with systemic lupus erythematosus (SLE) is particularly confusing. It is usually an occlusive microvascular disease that can lead to cotton-wool spot formation (areas of nerve-fiber layer swelling caused by ischemia) and occasionally to retinal hemorrhage. A more severe vaso-occlusive disease of larger vessels can also occur. Histopathologic studies show that vessels are occluded with amorphous hyaline material without evidence of inflammatory cells in vessel walls.[5] True retinal vasculitis is only rarely a feature of the disease. "Severe retinal vaso-occlusive disease" is probably a preferable name for this disorder.[6]

There are no well-established criteria for the clinical diagnosis of retinal vasculitis. Among the more useful definitions, however, is one proposed by Graham and co-workers.[7] They define retinal vasculitis as the vascular leakage and staining of vessel walls on fluorescein angiography, with or without the clinical appearance of fluffy, white perivascular infiltrates in an eye with evidence of inflammatory cells in the vitreous body or aqueous humor. When called on to examine a patient with "retinal vasculitis," it is appropriate for internists to ask the referring ophthalmologist if, in fact, the vascular disease appears to be inflammatory by these criteria. If

not, and it is solely an ischemic microvasculopathy—as manifested by cotton-wool spots, retinal hemorrhages, or both, without inflammatory signs—disorders such as diabetes, SLE or other connective tissue diseases, and even human immunodeficiency virus (HIV) infection (as discussed later) should be considered.

There are two goals in evaluating cases of retinal vasculitis. Ophthalmologists must assess the intraocular effects of vascular inflammation, and with their internist colleagues they should search for an underlying cause. The severity of damage to the retina and vision will direct the extent to which aggressive evaluation and therapy must be undertaken. Internists will be involved primarily in diagnosing and evaluating isolated cases of retinal vasculitis in which no other focal inflammatory lesions are found. Vasculitis is most commonly seen as an epiphenomenon in patients with other retinal disorders, such as ocular toxoplasmosis, cytomegalovirus retinopathy, or primary ocular disorders such as pars planitis. Because the vasculitis is not necessarily restricted to areas of the retina with primary disease, a careful search of the entire retina for focal lesions is critical in any patient with retinal vasculitis. In persons with toxoplasmic retinochoroiditis, retinal vasculitis has been shown to be an immunologic response to *Toxoplasma* antigens in the eye.[8,9] In this and other retinal infections, the vasculitis resolves without sequelae after appropriate antimicrobial therapy.

If no other retinal lesions are found, systemic inflammatory disease should be looked for. Despite the well-established association between retinal vasculitis and systemic disorders, a systemic illness is found in only a few cases.[10,11] In most large series, Behçet's syndrome and sarcoidosis are the most common systemic diseases identified.[10,11] Isolated retinal vascular inflammatory sheathing can occur in many diseases, but in disorders such as Crohn's disease,[12] Wegener's granulomatosis,[13] and polyarteritis nodosa,[14] it is much less common than are other ocular findings.

The acquired immunodeficiency syndrome (AIDS) has been added to the list of disorders associated with retinal vascular disease. A microvasculopathy similar to diabetic retinopathy is an almost universal finding in HIV-infected patients.[15,16] Infection of endothelial cells by HIV,[17] elevated circulating immune complexes,[18] and hemorheologic abnormalities[19] have all been hypothesized to be contributing factors. Isolated retinal vasculitis has been associated with HIV infection.[15] Although an uncommon manifestation in the United States, isolated retinal vasculitis is seen frequently among African patients with AIDS,[20] making it one of the distinctions between various patterns of HIV infection seen around the world.

Most cases of isolated retinal vasculitis remain idiopathic. The classic condition in this category is Eales disease, which may be a group of disorders characterized by peripheral occlusive periphlebitis without prominent inflammatory changes elsewhere in the eye. Described more than 100 years ago, its cause is still unknown. Furthermore, because specific criteria for the diagnosis of Eales disease have varied over the years, the term is not particularly useful.

A detailed description of inflammatory findings in the eye has limited diagnostic value with regard to retinal vasculitis. A distinction between retinal periphlebitis and arteriolitis can be made ophthalmoscopically but has rarely been emphasized in published series. Vascular changes vary widely among patients with any disease, but in most disorders the peripheral venules rather than arterioles are involved.[13,21,22] Syphilis is one disease thought to preferentially involve the retinal arterioles,[23,24] but both venules and arterioles can be affected.[23,25] The location and appearance of vascular lesions are also generally of limited diagnostic use. The term "candle-wax drippings" has been applied to dense, focal, nonocclusive periphlebitis associated with sarcoidosis, but its appearance is neither pathognomonic nor present in all patients with the disease. The occlusive phlebitis of Behçet's syndrome tends to manifest in the posterior pole, although peripheral retinal vasculitis may occur.

The laboratory evaluation should be directed by the patient's history and the findings of the physical examination. It is common for many ophthalmologists and their internist consultants to order a large, routine battery of tests for patients with ocular inflammatory disease, but this approach is rarely productive and can be misleading. For example, tests of anti-*Toxoplasma* antibodies are unnecessary in patients with isolated retinal vasculitis. As stated already, vasculitis can be a secondary finding in patients with focal necrotizing toxoplasmic retinochoroiditis, but the parasite does not cause retinal vasculitis alone. This fact, coupled with the high prevalence of anti-*Toxoplasma* antibodies in the general population, means that false-positive results are common with this approach.

There are very few laboratory studies that should be done in all patients with isolated retinal vasculitis. A VDRL and fluorescent treponomal antibody absorption test, or their equivalents, should always be done. Isolated retinal vasculitis is an uncommon manifestation of syphilis but one that should not be overlooked. A chest x-ray film to look for evidence of sarcoidosis or tuberculosis is also appropriate because these diseases may first be apparent in the eye.

The relationship between retinal vasculitis and *Mycobacterium tuberculosis,* however, is a source of confusion. It is well established that inflammatory sheathing of the retinal vessels can occur in patients with miliary tuberculosis and ocular infection. Retinal vasculitis has even been reported to be the first sign of disease in patients subsequently found to have active pulmonary tuberculosis.[26] A more difficult problem is the patient with isolated retinal vasculitis whose skin tests positive to purified protein derivative (PPD) without other signs of active ocular or nonocular tuberculosis. (Such an association has been described for many patients with Eales disease, but a causal relationship has never been established.) Some investigators advocate antituberculous therapy for such patients,[27] but this recommendation remains controversial. Because tuberculous uveitis without other signs of tuberculosis is extremely rare, other investigators simply refer patients for the management of their positive skin test, as they would do for anyone with this incidental finding. The retinal vascular lesions are then observed closely for the development of associated problems. The same does not apply to patients with both focal granulomatous lesions in the eye and retinal vasculitis; the granulomata would suggest localized infection.

Tests of immune function have been studied in large groups of patients with retinal vasculitis. Regardless of whether or not patients have evidence of associated systemic inflammatory disease, the most frequently identified abnormalities have been elevated circulating immune complexes and antibodies against retinal antigens, especially against the S antigen, a soluble protein located in the outer layers of the

retina.[7,11,28] Although not a universal finding in patients with retinal vasculitis, these abnormalities have given support to the hypothesis that retinal vasculitis is an autoimmune disorder. A causal relationship between such abnormalities and retinal vasculitis has never been established, however, and their role in the pathogenesis of the disorder remains speculative. Because these abnormalities have never been shown to have diagnostic, therapeutic, or prognostic significance,[29] they are probably unnecessary in the routine evaluation of retinal vasculitis.

The treatment of patients with retinal vasculitis should be directed toward the underlying systemic problem, if one is identified. Management of the vasculitis per se is necessary only if it is leading to vision-threatening complications. It is important to distinguish between vaso-occlusive inflammatory disease and simple vascular sheathing; fluorescein angiography is a useful tool in making this determination. Aggressive anti-inflammatory therapy is not indicated for patients with asymptomatic vascular sheathing; the use of steroids in such therapy may produce glaucoma and cataracts.

The treatment of occlusive vasculitis has generally been disappointing regardless of the modality used, but corticosteroids have been its mainstay. If there is no systemic disease, the periocular administration of long-acting corticosteroids such as triamcinolone acetonide should be considered to avoid systemic side effects. Topically applied corticosteroids cannot reach the retina.

Immunosuppressive therapy is usually a treatment of last resort, but the literature contains little evidence that it is beneficial for the long-term retention of vision in severe idiopathic retinal vasculitis. The use of immunosuppressive agents for intraocular inflammatory disease is generally reserved for patients with bilateral disease whose vision has fallen below 20/40 in the better eye. Occlusive vasculitis in patients with Behçet's syndrome is the one form of uveitis for which most authorities agree that immunosuppressive drugs are the treatment of first choice. They are best administered by an internist experienced in their use, with monitoring of treatment effect by an ophthalmologist, again indicating the importance of a team approach.

Sometimes complications cannot be avoided despite aggressive therapy. When complications arise, treatment with laser therapy for neovascularization or vitrectomy for hemorrhage is required.

More effective management of retinal vasculitis must await a better understanding of its associated disease mechanisms. Rosenbaum and colleagues have shown that progress is being made toward that understanding. In the meantime, they have provided an excellent framework for developing a rational approach to the current evaluation and management of the disorder.

GARY N. HOLLAND, MD
Associate Professor of Ophthalmology
Director, UCLA Ocular Inflammatory Disease Center
Jules Stein Eye Institute
University of California, Los Angeles, School of Medicine

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Modifying Physician Practice Patterns—Reflections on Past Deeds

THE PRACTICE OF MEDICINE once enjoyed a purity of focus that has only recently begun to change. The traditional physician knew that maximizing the welfare of patients was the order of the day. The health care system, having identified the physician as the patient's agent for that goal, fashioned itself to serve the physician's needs. What worked for the doctor worked for the patient. What worked for the doctor also worked for the hospital, at least for a while.

Now the picture has changed. Patients, physicians, and hospitals, while not having parted ways, have begun to identify their differences. Why has such a change occurred? Most observers agree on the spectrum of reasons, if not the magnitude of their contribution to the change. The explosion of technology with its heightened emphasis on uncertainty; changes in societal attitudes toward risk-taking, conflict resolution, and regulation; growing tensions between the demand for medical care and the supply of that care; and the

presence of new players (that is, payers) have all contributed to the partial dissolution of what once was seen as unity of purpose.[1,2]

With disarray, however, comes opportunity. Some of the same themes that have illuminated the differences among patients, physicians, and hospitals may also serve as the glue that binds them together. A common interest in quality, coupled with a desire for efficiency, has provided an impetus for new approaches to the delivery of health care services.

Among the approaches to achieving optimum cost-effectiveness, modifying physicians' practice patterns has drawn its share of attention. In this issue of the journal, Rosenstein and Stier describe a process—called the Medical Resource Management Program[3]—that relies heavily on the assumption that an important way to improve effectiveness and efficiency is to induce physicians to practice differently. There is little that is new in this assumption because it is known that physicians control the use of the majority of health care resources. What is different is the next assumption: that self-analysis will ultimately improve the efficiency of health care delivery. The emphasis here is on analyzing practice patterns, identifying areas that can be changed, educating about possible changes, and eventually implementing those changes.

Education has generally been viewed as the most desirable approach to modifying physician behavior, but its effectiveness in achieving that goal has been variable.[2,4-6] While a number of studies have shown that education about the prices or cost-effectiveness of various tests and procedures can result in a change in behavior, the economic effects of such changes have generally been modest at best.[7] The result is that other investigators have focused attention on other means of changing behavior: administrative barriers and penalties, incentives, and feedback about current performance.[2,5,8] In each case, there is evidence to suggest that these interventions are capable of inducing some degree of change. Again, however, the results are variable and often unpredictable. It has been argued that this unpredictability stems from several areas. First, the impetus for change often comes from outside the system and thus is resisted by physicians. The increasing development of practice guidelines is an example.[9] These guidelines are usually extremely general and may not fit the needs of the local setting. Second, the tools for change often do not involve practitioners. Physicians are asked to change their behavior but may not be asked how they feel about those changes. Often there are many competing forces that may work for or against achieving a desired goal. The authors of the change may be only vaguely aware of these forces, as opposed to the physician who will be strongly attuned to the presence and magnitude of each of the forces.

Keep in mind that physicians are extraordinarily capable of changing their practice when it seems appropriate to them. Witness the markedly diminished length of stay for acute myocardial infarction[5] and the rapid adoption of new technologies such as computed tomography and magnetic resonance imaging.[10] Most recently, in less time than it took to test whether or not extracorporeal shock wave lithotripsy of gallstones might provide a new way of treating gallbladder disease, physicians have nearly universally embraced laparoscopic cholecystectomy.[11] Given this evidence of rapid practice changes, why do we see strong resistance to other kinds of changes? As indicated earlier, most changes that deal directly with new approaches to cost-effective care involve understanding and manipulating a wide variety of complicated and potentially competing forces. As such, change is likely to occur only when it is driven on a local level where each force can be identified and understood. This is the strength of Rosenstein and Stier's approach.

While the approach proposed in their article is not new, it is still relatively untested. The authors describe the theoretical construct for what appears to be a promising system. Nonetheless, there is still only modest evidence that such an approach is economically justifiable. Earlier work has provided some evidence that change directed by self-analysis can have a substantial effect on selected aspects of practice. The Rosenstein model is an offshoot of an earlier project known as COSTEP, an acronym for "cost-effective practice." The COSTEP project, developed by Sommers and colleagues,[12-14] has now been applied in a number of hospital settings in northern California. In almost every case, the COSTEP project has been able to identify and significantly improve the efficiency of the delivery of care in well-circumscribed areas—length of stay in hip arthroplasty, fewer coronary care unit admissions for patients with chest pain, shorter stays of patients after a prostatectomy, and improved medication ordering for patients having cesarean section.

What do these successful projects have in common? First, they use good information.[15] That is, they have access to data about how care is provided and where potential problems may exist. Second, they depend on formalized reflection on actual practice patterns.[16] This can be viewed as a form of scholarly introspection. Next, they depend on reaching a consensus about how change might occur. There is some evidence to suggest that consensus is most likely to be reached when the instigators of discussion are respected leaders. Sommers and associates argue, moreover, that change is more likely to occur when the complete constituency for change is recognized. In many instances, this implies a closer working relationship between physicians and nurses, not just among physicians. Finally, there is the assumption that once a change occurs, its effect will be monitored through subsequent data analysis. In essence, we are talking about an action-experiment designed to change practice styles. Not only is such an approach theoretically sound, it is likely to be accepted by a wider group of practitioners.

Even then, will such a change make a true economic impact? That remains to be seen. Many physicians are cynical about the ability of any kind of practice change to have real economic effects, given the uncertain relationship between charges and actual costs. Perhaps the primary goal should not necessarily be the diminution of health care costs. In earlier years, physicians rarely concerned themselves with cost issues. While costs are an increasingly important concern to all members of the health care team, quality is still the primary goal. As long as the focus continues to be the efficient provision of high-quality care, it is likely that we will not stray far from the goal of providing cost-effective care. Is there really any other choice?

KEITH I. MARTON, MD
Department of Medicine
Pacific Presbyterian Medical Center
San Francisco, California

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Neuro-oncology Is Coming of Age

BIOMEDICAL RESEARCH is founded on the belief that insights into the cellular alterations that are responsible for pathologic disorders will provide a basis on which new approaches to the diagnosis and management of disease might be pursued. Recently, major advances in our understanding of tumor cell biology have dramatically expanded our knowledge of the molecular events that underlie the development of cancer, and these in turn have opened opportunities for the development of new therapeutic approaches not even imaginable a short while ago. The clinical conference in this month's issue of THE WESTERN JOURNAL OF MEDICINE describes new imaging and treatment modalities that hold promise for more effective treatment of patients with brain tumors.[1] Moreover, this report hints at the directions the next generation of studies may lead us. These future studies augur well for the likelihood that even more effective and less toxic approaches to therapy can be developed.

We now know that the panoply of cellular characteristics distinguishing malignant cells from their normal counterparts is orchestrated by the altered expression of genes important for normal cell growth and differentiation. Cancer arises as a disorder of genes. These genes are called oncogenes, emphasizing their importance in the development of tumors, and several have been implicated in the pathogenesis of brain tumors. Among the genes whose normal functions are used pathologically and contribute to the development of central nervous system (CNS) tumors are those that encode molecules important for the transmission of signals regulating cellular processes altered in tumor cells. For example, molecules on the surface of glial cells specifically bind small polypeptides capable of initiating the cascade of molecular events that becomes neoplastic growth. These molecules include the epidermal growth factor receptor and the platelet-derived growth factor receptors.

Membrane signal receptors for growth factors are under close scrutiny by investigators attempting to use them as targets for pharmacologic agents. The specific high-affinity binding of ligands to such receptors provides an efficient mechanism by which to expose tumor cells to molecules that can be imaged diagnostically and to cytotoxic moieties that can be used therapeutically. Cellular toxins, such as ricin, *Pseudomonas* endotoxin, and saprosin, as well as image-enhancing agents, have been conjugated to such ligands. The clinical efficacy of such "magic bullets" is currently being examined.

While such an approach has considerable appeal, investigators must overcome the binding of these hybrid molecules to comparable receptors on normal tissues. As pointed out in the UCLA conference report, it is now widely recognized that the benzodiazepine receptor exists in at least two distinct forms. One, the so-called central receptor, is found primarily in the CNS. A second, functionally distinct receptor, the "peripheral receptor," is prominent in many tissues throughout the body but expressed at only low levels in the CNS. This peripheral benzodiazepine is apparently expressed on glial tumor cells at levels as much as 20-fold higher than those seen on other central nervous system tissues. Interestingly, benzodiazepine ligands may be inhibitors of cell growth under some conditions, and the characterization of this growth regulatory ligand-receptor loop may provide insights into both the etiology and biology of glial tumors. Of immediate clinical import, however, is the possibility that this tumor-specific change might be exploited both diagnostically and therapeutically in studies attempting to target molecules to brain tumors.

If this quantitative difference in receptor expression is the result of enhanced expression of the receptor on all tumor cells, and not simply extremely high levels on a small proportion of malignant cells, it may provide the contrast required to target molecules and thereby distinguish malignant from normal tissue in imaging studies. Also, it may provide sufficient specificity to enhance the therapeutic index of hybrid molecules developed as antineoplastic agents to treat such tumors of the CNS. In this regard, expression of the peripheral benzodiazepine receptor on mitochondrial membranes is of particular interest because it raises the possibility that poisons that inhibit or alter the numerous biochemical processes that are limited to the mitochondria might be pursued as new antineoplastic agents. Of course, the hybrid molecules that would be designed for such targeted approaches to therapy would have to be taken up by CNS tumor cells. Also, the broad distribution of peripheral benzodiazepine receptor expression throughout the body will require the development of strategies to block binding at such sites if therapeutic applications are pursued. Pretreatment of patients with ligand bound to a molecule that could not pass the blood-brain barrier may be one such possibility.

New approaches to the imaging of brain tumors, also discussed at the UCLA conference, may provide additional opportunities to exploit tumor cell-targeted molecular manipulations, such as those mentioned. While surgical treatment and external beam irradiation remain our most effective modalities for the management of patients with brain tumors, their application could be greatly enhanced by a better understanding of the tumor-normal tissue interface. This information would allow more effective treatment with less toxicity. Positron emission tomography makes it possible noninva-

sively to map a variety of biochemical events in the CNS. As discussed in the conference summary, pituitary tumors have already been studied in this manner by targeting dopamine receptors with carbon 11-labeled *N*-methylspiperone. These studies demonstrate the feasibility of a receptor-mediated approach to visualizing malignant CNS tumors, and carbon 11-labeled ligands that bind the peripheral benzodiazepine receptor are now available for the examination of glial tumors.

Such an approach may complement current attempts to map tumor tissue metabolism, such as those that use fluorine 18-labeled fluorodeoxyglucose. While previous work has focused largely on the examination of neuronal activity and metabolism, the targeting of hybrid molecules that might specifically alter normal mitochondrial functions of glial tumor cells suggests that even a small number of cells might produce a distinctive signal. Such an approach could lead to more precise imaging of glial tumor tissues than is presently available by even the most sophisticated of techniques for structural mapping. Such information would complement the use of functional studies of neuronal tissue in planning more efficacious and less toxic approaches to therapy.

Better approaches to assessing the metabolism of normal and malignant cells of the CNS will also be important for the optimal evaluation of the various new approaches to therapy outlined in the final section of the symposium summary. This is particularly the case for invasive tumors of the CNS, which will never be optimally treated by local intervention that destroys normal tissue. If we are to exploit the important advances in molecular biology that suggest the possibility of developing new agents directed at restoring the tumor cells' capacity to regulate their own growth, noninvasive techniques to monitor treatment will be critical. The topics touched on by this conference foreshadow an exciting generation of clinical advances that can be anticipated based on ongoing genetic and molecular studies characterizing glial tissues and tumors. Advances of the recent past will undoubtedly be surpassed in even the near future.

MARK ISRAEL, MD
Brain Tumor Research Center
University of California, San Francisco
School of Medicine
San Francisco, California

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Myopathic Effects of Lovastatin

THE FIRST of a class of drugs that inhibit the rate-limiting step in cholesterol synthesis catalyzed by hydroxymethylglutaryl-coenzyme A reductase, lovastatin has been widely accepted and has become widely prescribed.[1] The growing awareness among practicing physicians of the enhanced risk of death from coronary heart disease caused by elevated blood cholesterol levels and lovastatin's relative freedom from side effects have contributed to its wide acceptance.[2] It was apparent from early trials, however, that this drug has the propensity to cause skeletal muscle injury.[3,4] This has been manifested chemically by elevated levels of creatine kinase in 0.5% to 2.0% of patients receiving the drug and clinically by muscle aches, tenderness, and weakness.[2] In a few cases, the muscle injury was more extreme, resulting in overt rhabdomyolysis and even renal damage.[5-8] Patients in whom rhabdomyolysis developed often were receiving other drugs including cyclosporine,[6] nicotinic acid,[8] and gemfibrozil.[7] Whenever it was measured, the concentration of the active drug in the plasma of patients exhibiting rhabdomyolysis was severalfold the therapeutic concentration, suggesting a disorder in the drug's metabolism.[2] These observations call for a brief review of the metabolism of lovastatin and the possible influence of drugs on it.

A fungal metabolite produced by *Aspergillus terreus*, lovastatin is a drug precursor that exists in the closed-ring lactone form.[9] After limited (30%) absorption from the small intestine, the drug is almost completely removed in a single pass through the liver where it is enzymatically hydrolyzed to its dihydroxycarboxylate or β-hydroxyacid open-ring form, which is the active inhibitor of cholesterol synthesis.[9] Only a small fraction of the administered dose appears in plasma, and only 25% of that is made up of active inhibitors, or less than 5%.[9] Most of the drug is excreted in the feces. With an appreciation of these characteristics of lovastatin metabolism, it becomes simple to envision how drugs or disease processes affecting hepatic cellular and enzymatic function can result in increased access of the drug to the peripheral circulation.

Cyclosporine is handled in the liver in a similar manner to lovastatin, namely, it is largely removed in the liver, metabolized, and eliminated in the bile.[10] Cyclosporine in high concentrations also can impair hepatic function.[10] It is understandable, therefore, that in a few cases where cyclosporine levels were markedly elevated and liver dysfunction was present, concurrent treatment with lovastatin resulted in clinical rhabdomyolysis.

Another group of drugs that are candidates for impairing lovastatin metabolism are the macrolide antibiotics, of which erythromycin is the most commonly prescribed member, especially in view of its efficacy against *Mycoplasma, Legionella, Chlamydia,* and *Campylobacter* species. Erythromycin is oxidized in the liver by the cytochrome P-450 enzyme system to its *N*-demethylated metabolite, which in turn forms an inactive complex with the iron ion of reduced cytochrome P-450.[11] This antibiotic has been shown to impair the metabolism of a variety of drugs,[11] including corticosteroids, theophylline, carbamazepine, warfarin, and, more recently, cyclosporine.[12] In our report of rhabdomyolysis and renal injury resulting from the use of lovastatin in conjunction with cyclosporine, one of the patients was also receiving erythromycin, and we cautioned about the potential adverse effect of using this drug.[6] In addition to a previous brief case report published elsewhere,[5] a case is reported in this issue of the journal of rhabdomyolysis culminating in renal failure and death in a patient with hepatic dysfunction receiving lovastatin who was treated with erythromycin for a pulmonary infection.[13] As in our patient, the open-ring free acid drug level was severalfold the therapeutic concentration. It is prudent to recommend, therefore, that lovastatin therapy be interrupted, or the dose drastically reduced, whenever a patient's condition necessitates therapy with agents that impair function of the cytochrome P-450 enzyme system or otherwise impair hepatic function.

Elsewhere in this issue of the journal is a report that demonstrates that 40 mg daily of lovastatin did not augment the modest increase in creatine kinase levels observed in healthy subjects undergoing eccentric muscle exercise.[14] In view of the foregoing discussion, this observation is not un-

expected. In the face of impaired drug metabolism and increased peripheral drug plasma levels, however, it could be that exercise will precipitate rhabdomyolysis.

WADI N. SUKI, MD
Professor of Medicine and of Molecular Physiology and Biophysics
Chief, Renal Section
Baylor College of Medicine and The Methodist Hospital
Houston, Texas

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 500 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Organic Cognitive Impairment?

To the Editor: An epidemic of local and systemic symptoms that followed the introduction of heat-cured phenol-formaldehyde resin in an aerospace plant generated public and professional disagreements over the cause of the outbreak.[1] Even though previous psychiatric evaluations were reported to have identified "brain damage," Sparks and colleagues have rejected the suggestion of organic brain effects among affected workers based on their use of an insensitive neuropsychological assessment of cognitive functions, and they have failed to present the data from those referred for the "standard battery of neuropsychological tests." In contrast to the thoroughness with which workers were screened for psychiatric diagnoses, screening for organic cognitive impairment was limited to "Folstein's Mini-Mental State examination, a brief test of cognitive ability,"[1] which has been criticized as "insensitive" because of "high false-negative rates" from "the reliance . . . on a global estimate of cognitive status (which) obscures the presence of isolated . . . deficits."[2] Since the usual pattern of cognitive function in mild chronic toxic encephalopathy is measurable impairment of only one or several specific types of cognition, use of a screening or diagnostic method that does not recognize such limited impairment would certainly mean that recognizable cases would be misclassified. Even with a relatively insensitive screening tool, Sparks and co-workers identified 4 persons with scores that indicated cognitive impairment. When these 4 and 21 others with symptoms of cognitive impairment were referred for detailed neuropsychological testing, however, "none were reported to have significant cognitive deficits of recent onset." This sequence is sufficiently unexpected that a more detailed presentation of data would have been in order. When their insensitive screening method produced positive results that were uniformly false, then the method in their hands did not have the "excellent reliability and validity" that they claimed. Their hypothesis that all cases were of psychosocial origin did not explain their four cases that were screened out as having cognitive impairment.

A reasonable alternative hypothesis could be that susceptible workers could have had mild organic cognitive impairment from which some could have recovered over periods of 4 to 12 months or more. Thus, examinations while the exposures were recent could have validly identified cognitive impairment, while a screening procedure done 6 to 12 months later could have shown that many no longer had cognitive impairment, and referral tests done an additional 1 to 3 months later could have shown that all tested had recovered, if such were the case. In this scenario no one would have to be accused of being wrong, but one would have to acknowledge that the final referral neuropsychological tests did not exclude organic cognitive impairment in the symptomatic period during and immediately after the exposures.

The authors claimed an absence of evidence for neurotoxicity of low-level formaldehyde exposure, which is contradicted by Kilburn and colleagues[3] and by Russian experience cited by Anger and Johnson.[4] Phenol is also neurotoxic.[4,5] Formaldehyde and phenol could have a synergistic neurotoxic effect.

We believe we have encountered cases of neurotoxic effects of phenol-formaldehyde resins in a different setting. We have seen fewer and more sporadic cases with unprotected exposures in poorly ventilated plywood or particleboard mills, usually resulting from periods of exposure of at least several years.[6] Our cases involved more men than women and produced objective effects on both central and peripheral nervous systems. Similar neurotoxic effects of phenol-formaldehyde resin have been reported from Russia[7] and Egypt.[8] We believe that Sparks and colleagues relied on an uncertain neuropsychological screening process, failed to consider the possible favorable prognosis of very mild cognitive impairment, and have underestimated the neurotoxicity of formaldehyde and phenol.

WILLIAM E. MORTON, MD, DrPH
Environmental Medicine Division, L352
Oregon Health Sciences University
3181 SW Sam Jackson Park Rd
Portland, OR 97201

ADRIANNE FELDSTEIN, MD, MS
Industrial Medicine Department
Portland Kaiser-Permanente Group
3600 N Interstate Ave
Portland, OR 97227

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Dr Sparks Responds

To the Editor: I appreciate the thoughts of Morton and Feldstein regarding our previous article on an outbreak of illness in aerospace workers.[1] I agree that Folstein's screen of cognitive function is relatively insensitive.[2] Of those who demonstrated abnormalities on the Mini-Mental State Examination, noncooperation, preexisting learning disabilities, or inattention due to depression could not be specifically addressed, as may be possible with a more detailed battery of tests combined with old school records or other data on baseline cognitive function.

We chose not to go into detail on the methodology and results of the more extensive neuropsychological testing done on a large proportion of the workers in our study, as we anticipate that this will be described in a future publication by the examining neuropsychologist.

The problems of population selection, methodology, and interpretation associated with Kilburn's study of histology technicians have been reviewed in several publications.[3,4] Also, neurotoxic effects of volatile organic compounds such as phenol are dependent on dose,[5] which in the case of the outbreak described in our paper was relatively low.

Much of the interpretation of the results of neuropsychological testing appears in the realm of art rather than science,[6] and the debate about whether subtle cognitive changes, temporary or persistent, may exist in workers with low-level exposure to phenol or other solvents will likely rage for years to come.

PATRICIA J. SPARKS, MD, MPH
Providence Medical Center
1600 E Jefferson, Suite 201
Seattle, WA 98122

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On-Line Medical Command

To the Editor: We are pleased to note that Hoffman and colleagues[1] have joined us in suggesting that paramedics should be allowed to exercise discretion in the use of on-line medical command (base command contact). Through review of cases comprising 28.4% of all contacts at their hospital, they determined that just 13 of 659 patients received "unanticipated therapies."

We analyzed 7,862 prehospital cases involving advanced life support of which 5,533 received on-line medical command; the remaining 2,329 cases were managed by protocol alone. For the 5,075 cases involving on-line medical command with no missing data, there were 176 occasions in which base command physicians deviated from standard treatment protocols.[2]

Our data reveal that of 2,232 cardiac cases that included lethal and nonlethal dysrhythmias, congestive heart failure, and chest pain of presumed cardiac origin, deviation from standard treatment protocols occurred on 121 occasions. Medical cases including seizure, syncope, abdominal pain, and altered mental status comprised 2,605 cases with physician-ordered deviation from protocol on 52 occasions. Trauma patients made up our smallest group—most of these patients did not receive on-line medical command—and of the 238 patients managed with on-line medical command, protocol deviations were ordered by physicians for only 3. In our study, physician discretion and resulting deviation from standard treatment protocols were more likely to occur among cardiac patients (121 of 176) than among those with complaints similar to the group studied by Hoffman (52 of 176).

Based on our experience we suspect that the sampling methodology used by Hoffman and colleagues leads them to overestimate unnecessary base command contacts at 90%. We estimate that an 80% reduction in calls may be possible.

Hoffman and associates estimate that reduced numbers of base command contacts could result in a cost reduction of $3 million out of a $7 million budget in Los Angeles. While that may be so in Los Angeles with its plethora of base command facilities, other systems with fewer base facilities would not achieve as great a cost reduction. Hoffman and colleagues' estimate is made without consideration for additional costs resulting from changing the system or the potential adverse effects of a discretionary system. Paramedics may not call when they should or they may reduce compliance with standard treatment protocols because they would be supervised less. To counter these potential effects, a retrospective medical control system that reliably measures paramedics' adherence to protocols and the effectiveness of their discretion in selecting those cases that require on-line medical command must be in place. Additional field supervision and training may be required. These are costly activities and would need to be included in the total costs of medical control, thus tending to reduce the economic savings from the reduction in use of on-line medical command.

Hoffman and co-workers' report contributes to the body of work that calls into question the efficiency and efficacy of mandatory use of on-line medical command. We agree that the efficiency and efficacy of its routine use must be evaluated rather than simply accepted as a routine practice. It seems to us that the accumulated evidence lays the foundation for a controlled study that will compare the cost benefits from a system with paramedic discretion to a compulsory system of on-line medical command.

Hoffman's paper was presented at the annual meeting of the Society of Academic Emergency Medicine (previously University Association for Emergency Medicine) in Minneapolis, Minnesota, during the May 1990 meeting, not 1989 as printed.

STEVEN J. DAVIDSON, MD, MBA
Professor of Emergency Medicine
Medical College of Pennsylvania
EMS Medical Director, City of Philadelphia
M. HAIM ERDER, PhD
Senior Research Scholar
Leonard Davis Institute of Health Economics
University of Pennsylvania
Research Instructor of Emergency Medicine
Medical College of Pennsylvania
3300 Henry St
Philadelphia, PA 19129

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* * *

Drs Hoffman and Schriger Respond

To the Editor: We are substantially in agreement with Davidson and Erder, whose data are basically concordant with our own. Given the experimental error inherent in any estimation of proportions based on a single group of subjects, we think their estimated reduction of 80% in unnecessary base command contacts only serves to support our own esti-

mate of 90%; these are statistically close enough, given the differences in our methods and the systems we analyzed, to strongly suggest the true rate is in the vicinity of perhaps 75% to 95%. With regard to associated reductions in cost, these will vary from place to place, and our estimate for Los Angeles cannot be automatically extrapolated to other environments with different configurations to their prehospital systems.

As we noted in our discussion, we think a system that relies primarily on off-line medical control (which is very different from a "discretionary system") offers tremendous potential advantages, including, ultimately, closer and more reliable supervision of paramedics than on-line systems. This does require, of course, as Davidson and Erder agree, a carefully constructed computer-based method of identifying any paramedic deviation from protocol.

JEROME R. HOFFMAN, MD
DAVID L. SCHRIGER, MD, MPH
UCLA Medical Center
Emergency Medicine Center
10833 LeConte Ave
Los Angeles, CA 90024-1744

Lyme Disease Surveillance in California

To THE EDITOR: Lyme disease is the leading tick-borne infection in California. Its frequency and location are difficult to assess, however. Lyme disease support groups and the media overestimate its frequency of occurrence. Conversely, the Centers for Disease Control (CDC) and the California Department of Health Services' (CDHS) figures for Lyme disease are misleadingly low. Official figures for California list 182 cases in 1987. The CDC had no tabulation for 1988 and 232 cases of Lyme disease in 1989.[1]

In contrast, a Northern California Lyme Disease Study* recorded 322 clinical cases in 1988 and 527 cases in 1989. Of these cases, 90% were reported from the counties north of the San Francisco Bay. This collaborative education and surveillance study was conducted with 501 participating office-based physicians in the 16 north Coastal Range counties of California, the major California locus of the transmitting tick vector, *Ixodes pacificus*. These physicians were sent the then-current CDC case definition of Lyme disease, ongoing current clinical review articles, literature abstracts, and interviews with Lyme disease experts. At the end of 1988 and 1989, a simple postcard report form was returned by 368 physicians. The clinical diagnosis of the treating physicians was accepted as the case definition for this study.

The low public health figure reflects surveillance before Lyme disease became a reportable disease in California in March 1989. Lyme disease will continue to be underestimated both in California and in other states using the CDC case definition, for several reasons:

- Physicians will not complete the required two-page CDC report form to report a basically noncontagious disease. This conclusion is reinforced by the experience of the Northern California Lyme Disease Study. In addition to the postcard report form, the study participants were requested to complete and return a more detailed cumulative report for their Lyme disease cases. Despite several reminders, only 167 of the 849 cases were reported on the detailed report form.
- The epidemiologic surveillance definition of the CDC for Lyme disease will exclude many clinical cases diagnosed and treated by a prudent physician. Requiring laboratory confirmation for all patients without erythema migrans ignores the vagaries of current serologic laboratory testing available to physicians in the field. Significant intralaboratory variance continues to be reported in the medical literature.[2,3] A test reported positive by one laboratory is reported negative by another laboratory. Until we have a standardized, readily reproducible test, Lyme disease will remain primarily a clinical diagnosis.

Even here, the CDC clinical criteria are so strict that any but classic manifestations will exclude many cases even with clearly positive serologic tests. In addition, the new CDC requirement of demonstrated intrathecal production of Lyme antibody will greatly reduce the reporting of a late manifestation of central nervous system Lyme disease. The laboratory testing for this is even less standardized and generally not available to physicians in the endemic areas of California. All of this can lead to the false impression that Lyme disease is a minor and lessening problem in California.

The CDHS estimate of the occurrence of Lyme disease in California would become more realistic if they would do the following:

- Accept Lyme disease reporting on the Confidential Morbidity Report form. This simple form, used for a host of other reportable diseases including far more serious ailments, would increase physician reporting compliance manyfold.
- Accept the clinical diagnosis of treating physicians as the Lyme disease case definition. This is done with a number of other reportable diseases. The CDC case definition is not mandatory and is not used in all states. Until we have an accessible gold standard test for Lyme disease, the clinical judgment of a physician who assumes responsibility for the diagnosis and treatment of a patient should remain paramount. The ubiquitous manifestations of Lyme disease make this judgment difficult. On the one hand, casual evaluation can lead to overdiagnosis and inappropriate treatment. Antibiotic treatment, both oral and intravenous, is a potent placebo. Symptomatic remission and exacerbation from this placebo effect can reinforce a false diagnosis of Lyme disease. The label of Lyme disease is difficult to remove and can delay the recognition of a correct diagnosis. Conversely, the failure to consider and test for Lyme disease can delay the proper treatment and relief of symptoms for many patients with less than classic symptoms. Lyme disease is truly the newest "great imitator."

Physicians should make the extra effort to use whatever form is required for reporting Lyme disease cases, even if they know the cases will not be counted.

ROBERT WERRA, MD
Coordinator
Northern California Lyme Disease Study
721 South Dora St
Ukiah, CA 95482

*The study originated from a grant by the California Institute of Family Medicine.

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Electromagnetic Fields and Cancer in Children—A Scientific Fact?

To the Editor: According to the journal, the purpose of the "Epitomes—Important Advances in Clinical Medicine" section is to help busy investigators and practitioners keep informed of items "that have recently achieved a substantial degree of authoritative acceptance." The journal also states: "Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established both as to scientific fact and important clinical significance."

The occupational medicine epitomes in the February 1990 issue include an assessment of studies linking electromagnetic field (EMF) exposure to an increased risk of cancer in children.[1] The inconsistency of findings reported by investigators working on this topic does not result in evidence of a "firmly established scientific fact" with a high degree of acceptance within the scientific community.

The 1979 study from Colorado referred to in the epitome, linking electrical wiring configurations and childhood cancer, has been criticized by many scientists. As just one example, Miller criticized the indirect measures of exposure and pointed out that a dose-response relationship, which had been suggested by the Colorado investigators, was not present.[2] Regarding possible confounding factors, one of the authors of the 1988 Colorado study subsequently found that the incidence of childhood cancer was associated with residential traffic density.[3] Increased risks for total number of cases of cancers and leukemias were related to increased traffic densities. The odds ratios for these associations were greater than those reported earlier for EMFs and cancer.

The epitome mentioned that "a study from Texas found a greater frequency of paternal occupations (electronics workers) involving exposure to electromagnetic fields among children who had died of neuroblastoma." But in another study (included in the epitome's list of references but not mentioned in the text), Nasca and colleagues stated that their data "failed to show any consistent association between childhood central nervous system tumor risk and paternal exposures to . . . electromagnetic fields."[4] In a subsequent study, Johnson and Spitz concluded that "if parental exposures in these industries are related in some manner to childhood tumours, the attributable risk, based on projections from our data, would be relatively low."[5] In fact, the highest risk estimate in their study was for construction electricians, who work mainly with unenergized wiring and thereby seem to have limited exposure to EMFs.

In studies of animals, the evidence for a possible cancer-promoting effect of EMFs is nonexistent or equivocal. Attempts to replicate initial reports supposedly supporting the hypothesis of carcinogenicity have been unsuccessful. To use the simple ubiquity of exposure to EMFs as a justification for further studies, even when there is no clear effect on public health, is questionable. Foster and Pickard, regarding bioeffects in a different range of the electromagnetic spectrum (specifically microwaves), have said that "such searches for hazards can go on too long, and guidelines for ending them must be established."[6] The same may be true for studies of EMFs at lower frequencies, as well. Cartwright pointed out that "so far not enough is known about EMF variability to be able to design useful studies to investigate EMF health effects. . . . With our present state of knowledge there is no justification for the massive expenditure. . . . Our present scientific knowledge points at the very best to a minute risk of EMF verging on the point of nonexistence."[7]

A few weak positive associations in epidemiologic studies do not constitute "important clinical significance," especially when additional studies showing no association are considered. The unsubstantiated claims of a link between EMF exposure and risks of cancer in children should not lead clinicians to believe that a hazard exists.

JAMES R. JAUCHEM, PhD
Research Physiologist
Radiation Sciences Division
US Air Force School of Aerospace Medicine
Brooks Air Force Base, TX 78235

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The views and opinions expressed herein are those of the author and do not necessarily state or reflect those of the US Government.

* * *

Dr Gold Responds

To the Editor: The letter from Dr Jauchem is welcomed for its illustration both of the complex and difficult nature of investigations in this field that often result in apparently conflicting findings and of the strength of responses generated to both positive and negative findings on this controversial subject.

Our original epitome was written to update clinicians and researchers on, and fulfilled the stated goal of keeping them abreast of, an active area of investigation and, though restriction on the length of epitomes precluded exhaustive review, to reflect the status of investigations up to the present time.[1]

"A few weak positive associations in epidemiologic studies" cannot be dismissed as having no clinical significance, even when there are additional studies showing no association. Weak positive associations can be important from both clinical and public health perspectives when the exposure of interest is highly prevalent, is of public concern, and when—as with childhood cancer—the potential outcome involves severe morbidity or lethality. As Rose points out, the relative risk estimate, to which scientists refer when discussing associations of exposures and disease outcomes, can be a misleading guide to policy.[2] Furthermore, as the calculation of population attributable risk reflects,[3] while the excess risk may be small, the total population attributable risk can be large if a sizable portion of the population is exposed. Thus, this is usually the more appropriate measure in making policy.[2]

The methodologic difficulties in conducting retrospective investigations of occupational and home electric magnetic field exposures were emphasized in the original epitome[1] and

have been reviewed in detail[4] and recently summarized.[5] Referring to the occupational studies, Pool says, "Individually, the various epidemiological studies can each be challenged on one ground or another, but as a group they have a rough consistency that is hard to ignore."[5] Thus, these studies illustrate the inherent difficulty of conducting research on the possible health effects of long-term, low-level exposure. As noted in the epitome, the methodologic concerns need to be addressed in better-designed studies, rather than regarding them as fatal flaws that preclude further investigations. Further credible research to understand any relationship of electric magnetic field exposures and adverse health effects is thus supported and encouraged.[5]

The claims that have been published regarding electromagnetic fields and cancer should not be characterized as "unsubstantiated," as the methodology of studies with both positive and negative results can be and have been criticized.[5] This will always be true because human studies do not—and ethically should not—deal with randomized controlled experiments to assess the relationship. Other causal associations (such as that of smoking and lung cancer) have been elucidated, even though their exact pathophysiologic mechanism(s) was not well understood at the time the association was affirmed.[2] This has not precluded developing and implementing effective preventive measures when the bulk of the evidence supports a causal association. If and when an excess risk of childhood cancer with electromagnetic field exposure is firmly established, it must also be determined to be a causal association, an endpoint that is not always clear-cut. Indeed, Rose points out that certainty and proof are inappropriate measures on which to base policy concerning public health: "Lack of proof is not in itself sufficient objection to action. . . ." He goes on to say, "direct observations of evident health effects should take priority over theoretical expectations,"[2] and, one might add, particularly when those health effects have potentially devastating outcomes.

ELLEN B. GOLD, PhD
Adjunct Associate Professor
Division of Occupational and Environmental Medicine
University of California
Davis, CA 95616

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1. Gold EB: Electromagnetic field exposure and risks of cancer in children, *In* Epitomes—Important Advances in Clinical Medicine: Occupational Medicine. West J Med 1990; 152:172

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Third World Plastic Surgery

To the Editor: In the last several years, an exponential growth has occurred in the quality and quantity of overseas charitable programs. It is estimated that 20% of plastic surgeons have donated their time and skills without charge to those in developing countries unable to receive care.[1] Specialists in orthopedics, ophthalmology, anesthesia, and maxillofacial surgery also participate heavily in these activities.

In plastic surgery, perhaps 400,000 operations have been done. With more than one surgical procedure per patient, almost 200,000 lives have been improved substantially. World relations have not suffered with this effort. Indeed, the hypothesis is that one person helping another is the best form of diplomacy extant in the world today.

Individual surgeons explain that the objectives of these programs are to provide an opportunity to help people, share knowledge with others, and form new professional relationships. Typically, participants say that the interchange challenges their full spectrum of training. Physicians feel as though they function as "real doctors" and are renewed in their excitement about their specialty.

Interplast, Reconstructive Surgery Foundation, African Medical Research and Educational Foundation (AMREF), Physicians for Peace, Operation Smile International, Interface-UCSD, Austin Smiles, Operation Rainbow, Operation Kids, Northwest Medical Team, and Southwest Medical Teams' Project Huasteca are some of the privately sponsored plastic surgery organizations dedicated to helping children who are not as fortunate as those in developed countries. The Plastic Surgery Education Foundation maintains a data base of volunteer organizations (call Andrea Contreras at 708-228-9900).

A child with a cleft lip or palate may be a pariah in the community, but a plastic repair may change a child who has little or no educational or social opportunity into a productive citizen. Our greatest goal is to see the recipients of our care become actual dispensers of care to other persons. "Give a boy a fish, he will enjoy a nice meal; teach him to fish, and he will not be hungry the rest of his life."[2] *Los barcos son seguros en los puertos; pero no fueron hechos para estar allí* ("The ships are safe in the harbors, but they weren't made to be there."[3] Doctors are comfortable at home, but they are trained to help people.)

DONALD LAUB, MD
1515 El Camino, Ober Bldg
Palo Alto, CA 94306

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Tryptophan and Eosinophilia-Myalgia Syndrome

To the Editor: In "Tryptophan-Induced Eosinophilia-Myalgia Syndrome" in the September issue,[1] Criswell and Sack suggest that in part, the pathogenesis of the eosinophilia-myalgia syndrome (EMS) could be related to an inhibition of interferon-gamma synthesis by tryptophan metabolites. Although we know of no one who has actually measured interferon gamma in this illness, there is considerable indirect evidence that interferon gamma and cell-mediated immunity are turned on in EMS. Data presented at the conference on the eosinophilia-myalgia syndrome in Los Alamos, New Mexico, in June 1990, as well as those published by Silver and colleagues,[2] show elevated serum levels of kynurenine, quinolinic acid, neopterin, and β_2-microglobulin with reduced levels of serum tryptophan. This pattern suggests an augmentation of the indoleamine-2,3-dioxygenase (IDO) enzyme system in macrophages (which is stimulated by interferon gamma)[3] and it mimics the picture seen

in cancer patients who have been treated with exogenous interferon gamma or interleukin 2.[4] The latter is a cytokine which produces significant eosinophilia.[5] Thus, in all likelihood the abnormal tryptophan metabolism seen in EMS patients is a consequence of the immune activation in this disease rather than the cause of it. Indeed, one might reason that an important factor in the pathogenesis of EMS may be an excess, rather than a deficit of interferon gamma. The observed active catabolism of tryptophan by the IDO pathway may well lead to a deficiency of tryptophan and serotonin. If serotonin does play a role in down-regulating interferon production as suggested,[6] this deficit of serotonin may lead to an unchecked increase in interferon gamma and result in excessive activation of macrophages and eosinophils as seen in EMS.

In addition, although tryptophan metabolism may play a role in the pathogenesis of EMS, epidemiologic studies point increasingly to a contaminant as the principal causal factor.[7-9] The recent identification of the chemical structure of one such contaminant[10] may soon lead to animal and in vitro models which will permit dissection of this most interesting syndrome.

PHILLIP A. HERTZMAN, MD
Los Alamos Medical Center
Los Alamos, NM 87544

RAYMOND R. BROWN, PhD
University of Wisconsin
Clinical Cancer Center
Madison, WI 53706

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* * *

Drs Criswell and Sack Respond

To THE EDITOR: We are pleased to respond to the thoughtful comments of Drs Hertzman and Brown. No one has measured interferon-gamma (IFN-γ) levels in patients with the eosinophilia-myalgia syndrome (EMS); thus, the finding by Silver and co-workers of elevated serum levels of L-kynurenine and quinolinic acid in such persons is unexplained.[1]

Interferon gamma can indeed stimulate indoleamine-2,3-dioxygenase (IDO), the rate limiting enzyme of the kynurenine pathway of L-tryptophan metabolism, but other substances such as endotoxin can also induce this enzyme. Furthermore, L-tryptophan influences the ability of IFN-γ to induce IDO.

Products of the indoleamine pathway of L-tryptophan metabolism, serotonin and melatonin, inhibit the production of IFN-γ. This may be important in the pathogenesis of EMS because IFN-γ is known to inhibit synthesis of collagen, the production of interleukins 4 and 5, and the production of IgE by B lymphocytes.[2-5]

It is likely that most, if not all, of the current cases of EMS are associated with a contaminant generated during the manufacturing of L-tryptophan. The manner in which L-tryptophan or a contaminant induces EMS is still open to speculation, however.

LINDSEY A. CRISWELL, MD
KENNETH E. SACK, MD
Division of Rheumatology
University of California, San Francisco, School of Medicine
400 Parnassus Ave, A-540
San Francisco, CA 94143-0362

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• Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
• Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
• Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

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• Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
• Gastrointestinal (mostly diarrhea): 2.5%
• Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
• As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
• Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
• Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

Abnormalities in laboratory results of uncertain etiology.
• Slight elevations in hepatic enzymes.
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(Continued from Page 167)

May 9-10—**New Mexico Medical Society Annual Meeting.** Albuquerque. Thurs-Fri. Contact: Glenn Taylor, NMMS, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or 1 (800) 748-1596.

August 5-9—**Body Imaging: Ultrasound, CT, MR, Nuclear Medicine.** El Dorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

February 15-19—**The 35th Anesthesiology Update** (Sponsor: UUMC). Fri-Tues. Snowbird. Contact: V. Larsen, (801) 581-6393.

February 17-20—**The 32nd Annual Ob/Gyn Update** (Sponsor: UUMC). Sun-Wed. The Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 19-22—**1991 Winter Ski Meeting and Ophthalmology Update** (Sponsor: UOS). Tues-Fri. Olympus Hotel, Salt Lake City. Contact: UOS.

February 19-23—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sun. The Marriott Hotel, Salt Lake City. Contact: (801) 588-2000.

February 19-23—**PALS Course** (Sponsor: UUMC). Tues-Sat. University of Utah, Salt Lake City. Contact: (801) 588-2000.

February 20-23—**Gynecologic Oncology and Surgery** (Sponsor: UUMC). Wed-Sat. The Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 20-23—**Physical Medicine and Rehabilitation Update** (Sponsor: UUMC). Wed-Sat. Radisson Inn, Park City. Contact: (801) 581-8664.

February 21-24—**Frank Walsh Society Annual Meeting** (Sponsor: UUMC). Thurs-Sun. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

March 4-8—**Advances in Internal Medicine** (Sponsor: UUMC). Mon-Fri. Snowbird. Contact: (801) 581-8664.

March 4-8—**Wilderness Medicine** (Sponsor: UUMC). Mon-Fri. The Cliff Lodge, Snowbird. Contact: (801) 581-8664.

March 8-9—**Human Sexuality/Spinal Cord Injury** (Sponsor: UUMC). Fri-Sat. Nursing Auditorium, University of Utah, Salt Lake City. Contact: (801) 581-8664.

March 16—**Hans Hecht Memorial Lecture** (Sponsor: UUMC). Sat. University of Utah, Salt Lake City. Contact: (801) 581-8664.

March 22-24—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

March 28—**Infofair** (Sponsor: UUMC). Thurs. Spencer S. Eccles Health Sciences Library, University of Utah, Salt Lake City. Contact: (801) 581-5762.

April 4—**Respiratory Tract Infections** (Sponsor: UUMC). Thurs. Deer Valley. Contact: (801) 581-8664.

April 5-6—**Hypertension** (Sponsor: UUMC). Fri-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

April 13—**Sports Medicine Update** (Sponsor: UUMC). Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

May 3-4—**Surgical Infections** (Sponsor: UUMC). Fri-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

May 10—**Ophthalmology, Annual Resident's Day, Clinical Conference** (Sponsor: UUMC). Fri. University of Utah, Salt Lake City. Contact: (801) 581-8664.

May 10-11—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

May 17—**Infectious Disease Update** (Sponsor: UUMC). Fri. Skaggs Hall Auditorium, University of Utah, Salt Lake City. Contact: (801) 581-8664.

May 30-31—**Communications Disorders** (Sponsor: UUMC). Thurs-Fri. Snowbird. Contact: (801) 581-8664.

June 9-11—**Interactive Video in Health Education—'Slice of Life'** (Sponsor: UUMC). Sun-Tues. University of Utah, Salt Lake City. Contact: (801) 581-8664.

June 17-21—**University of Utah School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Mon-Fri. University of Utah, Salt Lake City. Contact: (801) 581-8664.

July 8-13—**Update in Internal Medicine: Focus on Out Patient Medicine** (Sponsor: UUMC). Sat-Thurs. Snowbird. Contact: (801) 581-8664.

July 12-14—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

September 27-29—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
BYUHS:	Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.
DMC:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
SMH:	St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.
UMA:	Utah Medical Association, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUMC:	University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.
UVRMC:	Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

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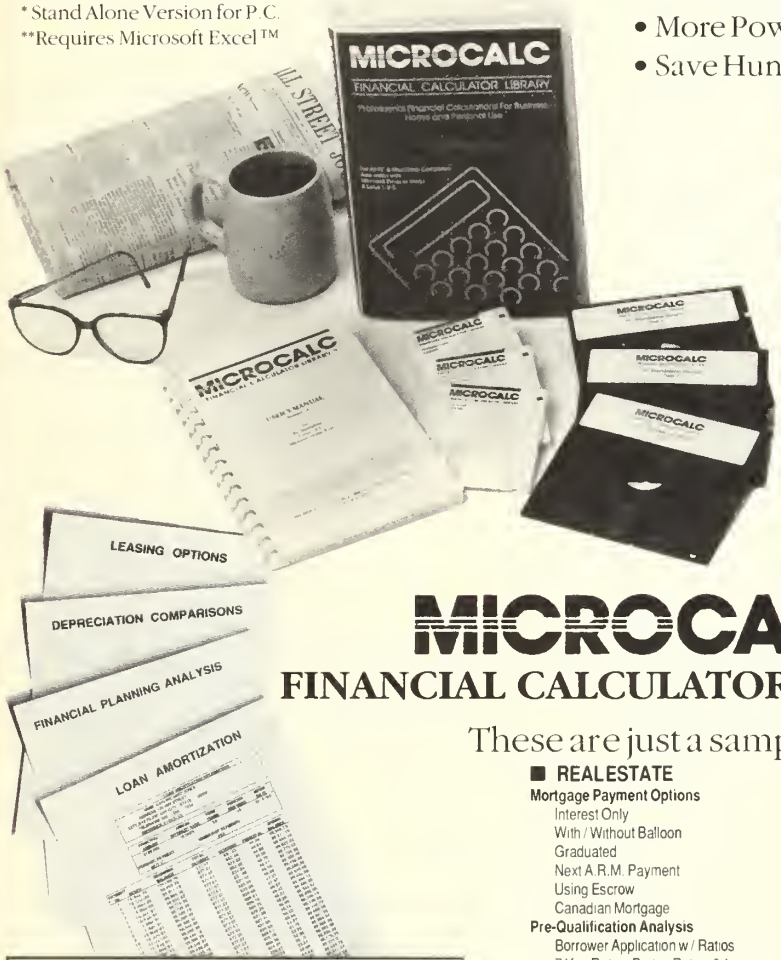

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WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

February 21-23—**Musculoskeletal Diseases for the Primary Care Physician.** Seattle. Thurs-Sat. Contact: U/W.

February 22-23—**Arthritis Update.** Seattle. Fri-Sat. Contact: U/W.

February 25-March 1—**AIDS Instructor and Program Development Course.** Seattle. Mon-Fri. Contact: U/W AIDS Education and Training Center, (206) 720-4250.

February 28-March 1—**A Day in the Office: Common Problems in Pediatric Practice.** Seattle. Thurs-Fri. Contact: Group Health, (206) 326-3441.

March 1—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 1-2—**Psychiatric and Psychological Issues in Medical Practice.** Seattle. Fri-Sat. Contact: VMMC.

March 8-9—**New Developments in Endocrinology.** Spokane. Fri-Sat. Contact: Spokane Society of Internal Medicine, (509) 448-2513.

March 13-15—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 14-15—**Tacoma Academy of Internal Medicine.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 14-16—**Emergencies in Older Patients.** Seattle. Thurs-Sat. Contact: U/W.

March 15—**Inflammatory Bowel Disease.** Seattle. Fri. Contact: VMMC.

March 22-23—**Ophthalmology (WSAO)—Annual President's Meeting.** Seattle. Fri-Sat. Contact: (206) 441-9762.

April 1-6—**General Practice Review.** Scottsdale, Arizona. Mon-Sat. Contact: Pacific Northwest Educational Institute, (206) 258-6322.

April 3-4—**Cumulative Trauma Disorders of Upper Extremities.** Seattle. Sun-Mon. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 4-5—**Aging and the Elderly.** Seattle. Mon-Tues. Contact: U/W.

April 11-12—**HIV/AIDS—Learning to Communicate Effectively to Reduce Patient Risk: An Experiential Workshop for Primary Care Providers.** Seattle. Thurs-Fri. Contact: U/W AIDS Education and Training Center, (206) 720-4250.

April 12-13—**Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS CME.

April 12-13—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 13-14—**Benton-Franklin County Medical Society Annual Meeting.** Tri-Cities. Sat-Sun. Contact: (509) 783-8616.

April 15-18—**The Best Approach 1991: Effective, Efficient Strategies in Cardiology, Orthopedics, Gastroenterology, and Pediatrics.** Kauai Sheraton, Hawaii. Fri-Mon. Contact: Group Health, (206) 326-3441.

April 15-26—**PM & R Review.** Seattle. Fri-Tues. Contact: U/W.

April 26-27—**Medical Issues of Active and Athletic Women.** Seattle. Fri-Sat. Contact: VMMC.

May 1-3—**ACP: Clinical Topics in Pulmonary Medicine.** Seattle. Fri-Sat. Contact: VMMC.

May 9—**OB/GYN.** Everett. Thurs. Contact: (206) 258-6322.

May 10—**Office Procedures.** Tacoma. Fri. Contact: PCMS.

May 11—**Corneal Update.** Seattle. Sat. Contact: VMMC.

May 31—**Office Gynecology—1991.** Tacoma. Fri. Contact: PCMS.

June 1—**Substance Abuse.** Seattle. Sat. Contact: U/W.

June 7-8—**Topics in General Medicine.** Seattle. Fri-Sat. Contact: VMMC.

June 15—**Horizons in Urology.** Seattle. Sat. Contact: U/W.

June 24-25—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: VMMC, (206) 627-7137.

July 26-28—**Seafair XII: Regional Anesthesia.** Seattle. Fri-Sun. Contact: VMMC.

August 9-11—**International Conference on Pancreatic Cancer.** Seattle. Fri-Sun. Contact: VMMC.

September 12-13—**Resolving the Ethical Dilemmas in Animal Protocol Review.** Seattle. Thur-Fri. Contact: U/W.

September 26—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

December 6-7—**Urology.** Seattle. Fri-Sat. Contact: (206) 441-9762.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact. Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 13-15—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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A Symposium on Human Health and Environmental Health

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For more information, call or write to:

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MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

OB/GYN. BC/BE to join 20 physician (OB, Pediatrics, Internal Medicine) practice in sunny central Washington. Reasonable call schedule with three OB/GYN department. Loan repayment program available. Competitive salary, excellent benefit package including vacation at 30 days per year and professional liability. Contact Ann Garza, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

MARYSVILLE (YUBA CITY). Primary care provider. Northern California primary care clinic. Three physicians, three physician assistants. No OB. No surgery. Near mountains, close to Sacramento, 2½ hours to Lake Tahoe and San Francisco. Salary $86,113 plus. Please contact Ed Allen, 938 14th St, Marysville, CA 95901; or call (916) 741-6244.

LOOKING FOR A PRIMARY CARE Internal Medicine Geriatric position with challenging and appreciative patients, quality associates, tolerable schedules in an attractive community? Send CV to Julie A. Prazich, MD, Medical Director, Sharp Senior HealthCare, 3545 Fourth Ave, San Diego, CA 92103.

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RADIOLOGIST. Part-time position available immediately in small hospital with general Radiography and Fluoroscopy, Mammography, and Ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

OREGON. General Internal Medicine and Family Practice, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

SAN FRANCISCO. Primary Care Practice in Noe Valley seeks BC/BE Family Practitioner or Internist to join growing practice. Competitive salary, wonderful neighborhood, partnership option. Send résumé to Noe Valley Family Medicine, 3700 24th St, San Francisco, CA 94114.

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ENDOCRINOLOGIST
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- **FAMILY PHYSICIAN.** Join busy Family Practice group (four Family Practitioners) in private practice. Salary or guarantee first year.

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COASTAL CALIFORNIA 45,000 population. Well-trained 12 physician Primary Care group. Immediate/future need for Family Practice and Internal Medicine. Competitive salary and benefits with partnership after one year. On call schedule allows time for family and recreation. In Lompoc, you can do what you were trained to do, including OB, Pediatrics, and General Medicine. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

PEDIATRICIAN, BC/BE to join group Family Practice/Pediatrics. Growing community with growing pediatric population. Active Nursery Level II hospital and nursery with NNP coverage. Offering competitive salary, equal call schedules, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

MEMORIAL CLINIC offers excellent opportunity for BC/BE Family Practitioner to establish a second Family Practice neighborhood clinic. OB optional. Competitive salary and excellent benefits. Send CV to Memorial Clinic, Attention Inge Hart, 500 Lilly Rd, N.E., Olympia, WA 98506; (206) 456-1122, ext 249.

WASHINGTON, PUGET SOUND. Part- or full-time Emergency Department practice with low volume, excellent medical staff, and great freedom of scheduling. Malpractice paid. Independent contractor. Send CV to TECP, 955 Tacoma Ave S., Ste 210, Tacoma, WA 98402.

(Continued on Page 238)

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AIR FORCE

(Continued from Page 236)

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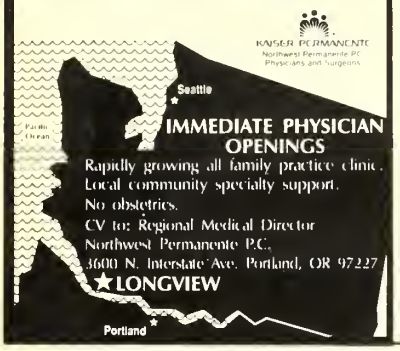
LONGVIEW, WASHINGTON



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OCCUPATIONAL MEDICINE—SAN FRANCISCO BAY AREA. Area's leading multispecialty private group practice is seeking a BC/BE primary care physician to join their expanding Department of Occupational Medicine. Range of practice includes pre-employment physicals, diagnostic evaluations, treatment of on-the-job injuries. If you are interested in building a career in Occupational Medicine, we will provide comprehensive training. Competitive salary, plus incentive, excellent benefits, paid malpractice. Located in the south bay which offers wonderful cultural/recreational activities, fine dining, outstanding climate and scenery, easy access to beach and mountains. For further information, please send CV or contact Maureen Forrester, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112; (408) 282-7833.

OCCUPATIONAL MEDICINE PHYSICIAN. Modesto Occupational Medical Clinic is looking for a full-time physician. We are a young, thriving high-volume practice in need of an additional physician who is BC/BE or with experience in Occupational Medicine. We are a full service clinic with x-ray, Physical Therapy, and all equipment for Occupational Monitoring. We have a large client company base with several years of experience. This person must have good clinical skills, be highly motivated, be energetic, and looking for a challenging career. Position may include administrative and clinic responsibilities with opportunity for partnership. We are located in the central valley two hours from both San Francisco and several excellent ski resorts in the Sierra Nevada. Please contact Susan Hooper, 1600 Sunrise, Ste 16, Modesto, CA 95350; (209) 529-6234.

ORTHOPEDIC SURGEON. University of California, San Francisco seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position at the Valley Medical Center, Fresno. The Orthopedic Department at VMC supports a busy Trauma Service and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. This position also offers private practice opportunities in a setting within the faculty group. Competitive salary and benefits. The central California location offers affordable and enjoyable year-round recreational living. Address inquiries and CVs to H. B. Morgan, Jr, MD, Chief of Orthopedics, 2212 N. Winery, #130, Fresno, CA 93703. EO/AA employer, women and minorities are encouraged to apply.

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SAN FRANCISCO EAST BAY. BE/BC Internist needed to join ten physician Primary Care group practice in beautiful San Ramon Valley area. Excellent opportunity and compensation. Reply in confidence to Number 223, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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WARM AND SUNNY ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 145 plus physicians in 14 clinic locations throughout Arizona has positions available in Family Practice, Internal Medicine, Pediatrics, and Orthopedics. Exceptional fringe benefits, profit sharing, and retirement program. Guarantee for first two years, plus incentive. Early shareholder. Fee-for-service, as well as physician owned HMO. Must be BC/BE. Call or write Bill De Long at Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; 1 (800) 658-9166.

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(Continued on Page 239)

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CALIFORNIA
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GENERAL INTERNIST IN THE PACIFIC NORTHWEST. Busy 30 doctor multispecialty group practice looking for General Internist with ICU skills and interests to join an existing Internal Medicine department. Competitive salary and benefits; ownership status available after 18 months of employment. Send CV to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

DENVER—FAMILY PHYSICIANS. Opportunities now exist for Family Physicians in the Denver suburbs of Aurora and Thornton. Several solo Family Practitioners and groups, including MDs and DOs, are now seeking additional members. For more information, send your CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-2A, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

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SEATTLE, Washington suburban 26 physician primary care group has immediate need for Family Physicians and Internists. Area growth has created the need for a team physician who enjoys work as well as play in the beautiful (and affordable) Pacific northwest. Remuneration includes salary, bonus, and fringe benefit package. For more information, please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

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(Continued on Page 240)

(Continued from Page 239)

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SOUTHERN CALIFORNIA EMERGENCY PHYSICIANS

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for staff positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

NORTHERN CALIFORNIA—INTERNAL MEDICINE. The Permanente Medical Group is seeking a BC/BE Internist to join their thriving practice located in Redwood City. Critical care experience helpful but not crucial. We offer a highly competitive salary and a substantial benefits package which includes malpractice insurance, medical, dental and group life insurance, educational leave, an excellent retirement program and a desirable San Francisco bay area location. Please respond with CV to Norman Olson, MD, Chief, Department of Medicine, 1150 Veterans Blvd, Redwood City, CA 94603. EOE.

FAMILY PRACTICE, SAN DIEGO. Join a seven physician group—all Family Practice, great location. Good pay and benefits. No Obstetrics. Contact Andrea Bower, MD; (619) 745-2000, 815 E. Pennsylvania Ave, Escondido, CA 92025.

NORTHERN CALIFORNIA—SAN FRANCISCO BAY AREA. Leading HMO is seeking BC/BE physician to staff a busy, urban, full-service Emergency Department with the possibility of administrative advancement. Kaiser Permanente is a large pre-paid HMO offering competitive salary, job security, shareholder status and generous benefits including health care, life insurance, disability insurance, sick leave, mortgage assistance, and educational leave. Please address all inquiries to David Witt, MD, Emergency Department, Kaiser Permanente Medical Center, 1200 El Camino Real, AD-WJM, South San Francisco, CA 94080-3299; or call (415) 742-2516. EOE.

TWO INTERNISTS seek an associate BE/BC Internist for busy Internal Medicine group practice located in a community of 60,000. Forty miles from San Francisco. Excellent modern hospital. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

A BE/BC NEPHROLOGIST is needed to join a two doctor practice in Nephrology forty miles from San Francisco. Excellent modern hospital with Chronic Dialysis unit next door. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

CHEYENNE, WYOMING. Immediate opening available for a dedicated, career oriented, full-time physician with Urgent Care facility in Cheyenne, Wyoming. Competitive compensation plus malpractice insurance. Approximately 14 days per month, standard 12 hour shifts. Excellent living conditions, high quality school system, moderate taxes and living expenses, exciting recreational opportunities in the heart of the Rocky Mountain region. Call now for additional information or send CV to Janet Cowley, Recruitment Coordinator, PO Box 805, Cheyenne, WY 82003; call toll-free, (800) 877-1436, or (307) 632-1436, FAX (307) 635-4642.

EMERGENCY MEDICINE. Emergency Medicine group seeking career oriented ACLS, ATLS certified physician for an immediate opening. Moderate volume; income $140,000 plus. Great outdoor activities including hunting, fishing, boating, skiing, sailing, camping, and hiking in south central Washington on the Columbia River. Send CV to Kennewick Emergency Physicians, PS, PO Box 6192, Kennewick, WA 99336-6192; or call (509) 627-1798.

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Two doctor ENT office. Senior member retiring in July of 1991. BC/BE.

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Area brochure available upon request.

WASHINGTON—PUGET SOUND. Semi-rural clinic needs Primary Care physician, Internist, or Family Physician. Part-time or possibly full-time. Fully equipped facility, close to Olympia and Tacoma, active practice, no Obstetrics. Send CV and references to Karl Champion, PO Box 760, Yelm, WA 98597.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

CENTRAL CALIFORNIA. Hospital based teaching opportunity for OB/GYN in a new residency program at the KMC. Ideal candidate is a team player with a strong desire to teach residents. This UCLA affiliate has a busy OB department with 5,000 deliveries per year. Please contact Mary Letterii, Vice President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

CENTRAL CALIFORNIA. Anesthesiologist Medical Director needed for high volume teaching hospital. Opportunity to develop contract for services with Kern County. Successful candidate has good track record of leadership with solid clinical background. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

CURRENTLY RECRUITING for Physician Administrator at Los Lunas Hospital and Training School, Los Lunas, New Mexico; a 350-bed state facility for the developmentally disabled. Requirements include MD plus four years medical practice; New Mexico license. Extensive knowledge of management of health care facilities. Good benefit and retirement package. Up to $76,949 (no liability insurance needed). Applications are now being accepted. Call David LaCourt, PhD, Administrator, at (505) 841-5264 for application and more information.

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Winslow Wong, MD
Attn: Administration
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545

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UNIQUE CLINICAL INTERNAL MEDICINE FELLOWSHIP. UCLA Department of Medicine offering fourth year training in Internal Medicine, through the Kennamer Fellowship, supported by the Albert Parvin Foundation. Fellowship begins July 1, 1992 for candidates BC/BE in Internal Medicine. A one year fellowship for practice careers. One fellow will be based at each of UCLA's major affiliates: Cedars-Sinai, Harbor, UCLA-San Fernando Valley, UCLA and Wadsworth/VA. Stipend is $33,500 plus the benefits program available at base hospital you choose. For forms and details write Roy T. Young, MD, UCLA Department of Medicine, 32-115 CHS, 10833 Le Conte Blvd, Los Angeles, CA 90024. Applications deadline April 30, 1991. Interviews by invitation. All applicants notified before July 1, 1991. Equal Opportunity/Affirmative Action Employer.

BC/BE FAMILY PRACTITIONER, OB-competent, for nonprofit community clinic in California redwood country. Rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

PHYSICIANS—PHOENIX, ARIZONA. Join six other physicians in providing comprehensive medical care for a 550-bed psychiatric hospital. Benefits include a generous pay schedule ($80,000 to $100,000 per year starting salary), regular daytime hours, no call or weekend duties, and an optional four-day work week. Interested applicants should send CV to Greg Maynard, MD, Director Medical Department, Arizona State Hospital, 2500 E. Van Buren, Phoenix, AZ 85008; or call (602) 244-1331.

JUNIOR FACULTY INTERNIST. University of California, San Francisco, Valley Medical Center, Fresno Medical Education Program, Department of Family Practice seeks recent BE Internal Medicine graduate to attend on a general Internal Medicine ward, teach in the ambulatory setting and contribute to the intellectual life of the Department. Our full-time experienced Senior Internist will provide faculty development, consultation, and backup. VMC is a major affiliate of UCSF School of Medicine sponsoring several well regarded programs, including Internal Medicine. Delightful and affordable central California location. Salary guarantee and faculty practice plan incentive. Available July 1, 1991. Send CV to Robert Heiligman, MD, Assistant Chief of Family Practice, 2212 N. Winery, #130, Fresno, CA 93703. EOE, women and minorities are encouraged to apply.

RADIOLOGIST—SAN FRANCISCO BAY AREA. Growing outpatient imaging practice with CT/MRI. Salary leading to partnership. Send CV to Murray Solomon, MD, 450 Sutter St, Ste 835, San Francisco, CA 94108; (415) 296-8654.

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TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7153, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

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(Continued from Page 240)

ORTHOPEDIC SURGEON

BC Orthopedic Surgeon needed for office practice in beautiful southern California area. Full- or part-time, surgery optional. Excellent compensation package. Send CV to **Ronald Gilbert, MD, c/o Gilbert Medical Group, 1076 E. First St, #A, Tustin, CA 92680; or call (714) 832-1516.**

MEDICAL DIRECTOR TRAUMA SERVICES. Eden Hospital. Level II Regional Trauma Center, Alameda county. Available December 1, 1990. Submit CV to Trauma Services, Eden Hospital, 20103 Lake Chabot Rd, Castro Valley, CA 94546; or call Dr Peter Wong, (415) 886-0535 or Dr Brian Walker, (415) 881-8445.

COLORADO. BC/BE INTERNIST to join three Internists in multispecialty group. Excellent opportunity for person interested in rural living, mountain recreation, and health care for medically underserved population. Send CV to Marguerite Salazar, 204 Carson Ave, Alamosa, CO 81101; (719) 589-5161.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Room Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

SEATTLE: BC/BE General Internist to join BC Internists' group with three Seattle area offices. No income guarantee; group and location excellent. Call or write Douglas Bovee, MD, 3203 W. McGraw, Seattle, WA 98199; (206) 285-3139.

SOUTHERN CALIFORNIA NEUROSURGEONS

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for staff positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

SAN JOSE, CALIFORNIA. Family Practice, Internist, Pediatrician, Psychiatrist, BC/BE. For full-time position in the Santa Clara Valley at Agnews Developmental Center. Join 17 physicians in the care of the developmentally disabled. 40 hour week, with some night and weekend calls, generous retirement and health benefits. California license required. Contact Karen I. Kral, MD, Medical Director, 3500 Zanker Rd, San Jose, CA 95134; (408) 432-8500.

RADIOLOGIST needed to perform state-of-the-art Diagnostic Radiology. Salary $100,000 per year. Minimum requirements are an MD degree, Radiology Board Certification, Utah Physician Surgeon License, and ability to perform MRI, Cardiac Ultrasound, selective Angiography, and invasive procedures requiring Angiography. Job located in Tooele County and Salt Lake County, Utah. Contact D. Michael Edson, MD, President, Consultant Radiologists, 3460 S. Pioneer Parkway, West Valley City, UT 84120.

INTERNIST. Immediate opening. Large, established, rapidly growing Los Angeles medical facility. High salary. Full benefits. Malpractice insurance paid. Contact Mr Miller; (213) 384-2504.

PEDIATRICIAN

Multispecialty group located in San Luis Obispo, California, seeks BC/BE physicians. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to **Physician Recruitment, San Luis Medical Clinic, 1235 Osos St, San Luis Obispo, CA 93401.**

CARDIOLOGIST. Invasive, including Angioplasty. BC/BE, full-time. San Mateo County General Hospital. Send CV and three references to Allen C. Lapin, MD, 222 W. 39th Ave, San Mateo, CA 94403; (415) 573-3786.

INTERNIST WANTED. Internal Medicine physician wanted to join an Internal Medicine group in San Diego, California. Guarantee plus commission. Opportunity to join full partnership in two years. Reply to Number 231, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

DENVER—INTERNIST. A busy two physician group, established in high-growth suburb since 1976, is now seeking a third member. For more information, send CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-2B, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

OREGON. Family practice opportunity in group practice in scenic area in Oregon's coast range. Within one hour of the ocean, this location offers excellent steelhead fishing, hunting, ranching, etc. Hospital provides complete relocation assistance. Oregon provides tax incentives to physicians in rural practice. Contact Jean Erickson, 305 NE 102nd Ave, Portland, OR 97220; (800) 622-3377.

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OBSTETRICS/GYNECOLOGY SOUTHERN CALIFORNIA: KAISER PERMANENTE

Join the nation's largest physician-managed, multispecialty medical group. We offer a choice of professional environments ranging from a 250-bed community hospital to a major teaching facility, highly competitive income, paid malpractice insurance, and much more. Send your CV to:

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FAMILY/GENERAL PRACTICE POSITION. We are looking for a Family/General Practitioner to join a progressive small group practice in Berkeley, California, serving a very diverse patient population. We practice a wide range of adult medicine, general hospital medicine, office Pediatrics and Gynecology. There is no Obstetrics. Work hours are flexible and range from half- to full-time. The starting date and salary are negotiable. Minorities and women encouraged. Contact Linda Spangler, MD, Alcatraz Ave Medical Group, 1650 Alcatraz Ave, Berkeley, CA 94703; (415) 652-8680.

FACULTY POSITIONS. Well established, fully accredited, 18 resident program seeking full-time faculty. Program is affiliated with UC Davis and located in Stockton, California. Candidate must be BC/BE. Teaching and OB experience preferred, but not required. Responsibilities include resident teaching, patient care, administration, and research development. Send CV to Bruce S. Nickols, MD, Family Practice Department, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6834. AA/EOE.

CALIFORNIA. Immediate permanent placement opportunities in Internal Medicine, Plastic Surgery, Urgent Care, Pediatrics, Otolaryngology, and Family Practice. For information call/send CV to Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, fax (415) 376-0813.

BC/BE PEDIATRICIAN WANTED for semi-rural community 25 miles south of San Francisco to associate with five member Family Practice group. Send inquiry with CV to Lawrence Bruguera, MD, Coastside Medical Clinic, 225 S. Cabrillo Hwy, Ste 100-A, Half Moon Bay, CA 94019.

OPPORTUNITY for full- and part-time Emergency Physicians. Excellent fee-per-patient load ratio. Malpractice paid. Also, Emergency Department/Family Practice positions for urgent care/industrial center. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is searching for physicians residency trained or BC in Emergency Medicine. The Health Science Campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level One Trauma Center, has paramedic base station training responsibilities, and has a helicopter service. An approved Emergency Medicine Residency Program began in July 1990. Emergency Physicians supervise medical students, interns, and residents, in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive, and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

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SOUTHERN CALIFORNIA (San Diego County). Thriving coastal city of Encinitas. Three Physician Family Practice Group plus Psychologist seeking residency trained Family Practitioner. Located in new Primary Care/Multispecialty full service facility eight minutes from hospital. Send CV to NCFMG, 477 El Camino Real, A306, Encinitas, CA 92024.

INTERNAL MEDICINE—Nevada, Texas, Louisiana, Florida. Private practices available with established physicians or groups. For details, call Eloise Gusman; 1 (800) 535-7698 or send CV to PO Box 1685, Covington, LA 70434-1685.

OTOLARYNGOLOGIST—DENVER. A successful and well-established ENT practicing in a fast-growing suburb of Denver is now seeking an associate (MD or DO) so he can open a second office. Six-figure first year guaranteed income with future partnership. Send CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-2C, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

THE DIVISION OF FAMILY MEDICINE at the UCSD School of Medicine is recruiting physicians to staff clinical practices and to provide clinical supervision to residents and medical students at a variety of locations in San Diego county. Candidates should be BC in Family Medicine and licensed or eligible for licensure in the state of California. Responsibilities will include direct patient care. Salaries are competitive and commensurate with experience and qualifications. Candidates should send a CV and names of three references to David M. Baughan, MD, Director of Clinical Services, Division of Family Medicine (0807) UCSD, 9500 Gilman Dr, La Jolla, CA 92093-0807. The University of California, San Diego is an Equal Opportunity/Affirmative Action Employer.

UNIVERSITY OF NEVADA SCHOOL OF MEDICINE, Reno-Lake Tahoe, seeks General Internal Medicine Clinic Director, assistant to full professor. Responsibilities include supervising and teaching residents and students, limited direct patient care, administration, and research options. Must be BC/BE Internist, eligible for Nevada licensure. Send CV and names of three references to Stanley Shane, MD, Department of Internal Medicine, 1000 Locust St, University of Nevada, Reno, NV 89520. Search will continue until position filled. AA/EOE.

SAN JOAQUIN VALLEY. Excellent opportunity for Family Practitioner to serve the underserved. No night call or weekends. Competitive salary plus benefits, paid malpractice. Agricultural community, one hour from the mountains, two hours from the coast. Bilingual English-Spanish helpful. Send CV to Hugh F. Stallworth, MD, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

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An immediate need exists to join this busy Family Practice adjacent to Northwest Hospital in the newly completed medical office building. Call and coverage is one to five. A generous salary, plus bonus and expenses, is provided. Should you require additional information, please call:

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or forward your CV to:

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CALIFORNIA—NAPA. Attention General Practitioners, Family Practitioners, Internists, Emergency Room Physicians: Napa State Hospital has two full-time positions for medical/surgical on-duty coverage, 4:30 pm to 8:30 am (16 hour shift, ten days per month). No responsibility for psychiatric call. Salary $77,472 to $85,224 annually, with raise on January 1, 1991. Benefit package approximately 33% additionally. Napa State Hospital has a large (100 plus) well trained medical staff, intensive on-campus CME, and a university affiliated research unit. EOE, Affirmative Action, physicians union. Send CV to Jeffrey Zwerin, DO, Medical Director, Napa State Hospital, 2100 Napa-Vallejo Hwy, Napa, CA 94558-6293; telephone (707) 253-5434. In California; 1 (800) 421-0666.

PEDIATRICIAN—Salt Lake City area. Progressive community, excellent cultural and recreational opportunities. Thriving multispecialty practice or solo practice location. Top remuneration. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

OB/GYN—Salt Lake City area. Progressive community, excellent cultural and recreational activities. Thriving independent practice in multispecialty group location with excellent coverage. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

COASTAL SOUTHERN CALIFORNIA. Seeking BC/BE Internist with subspecialty in Oncology to join a fast growing multispecialty group practice in north San Diego county. Generous compensation package; competitive salary, malpractice, medical/dental/life/AD&D/disability; wonderful living environment. Please send CV to Physician Recruitment, The Mission Park Medical Clinic, 2201 Mission Ave, Oceanside, CA 92054; or call (619) 967-4892.

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Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

FAMILY PRACTICE-HOSPITAL SPONSORED CLINIC OPPORTUNITY. Dynamic, growth oriented hospital in beautiful north central Wisconsin is seeking Family Physicians to join a growing practice in a new facility. The administrative burdens of medical practice will be minimized in this hospital managed clinic. The hospital has committed to an income and benefit package which is significantly higher than similar opportunities. Package includes base income, incentive bonus, malpractice, disability, signing bonus and student loan reduction/forgiveness program. All relocation costs will be borne by the hospital. Please contact Kari Wangsness, Associate, The Chancellor Group, Inc, France Place, Ste 920, 3601 Minnesota Dr, Bloomington, MN 55435; (612) 835-5123.

RADIOLOGIST NEEDED to join one other in a 60-bed hospital based practice with GE 1.5 MRI, 9800 CT, Doppler US, SPECT nuclear, angiography. Excellent salary leading to early partnership. Unique opportunity to join a sophisticated practice while living among the redwoods in a northern California coastal city with a referral population of over 100,000. Send CV to Dr Jackson, 3560 N St, Eureka, CA 95501; (707) 445-5993.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

OBSTETRICS/PEDIATRICS. Small multispecialty group seeks second Pediatrician and OB/GYN to work with present physicians. Excellent compensation and benefits. Looking for long-term partnership. Call or send CV to Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

INTERNIST—Salt Lake City area. Progressive community, excellent skiing, hiking, as well as close proximity to major city. Independent or multispecialty group locations. Outstanding remuneration package. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

INTERNAL MEDICINE. Full-time BC/BE Internist for multispecialty group in southeast Los Angeles. Office/hospital and consulting practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for partnership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

SAN FRANCISCO bay area Internist/Endocrinologist needs associate. Full- or part-time. Respond to Number 233, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ARIZONA—VA Medical Center, Prescott, Arizona, imaging service is accepting applications for a full-time Radiologist. Competence and proficiency in interpreting CT scans is required. Prescott is a 217-bed general medicine hospital with a busy combined Radiology and Nuclear Medicine service. Prescott is located in the mountains of north-central Arizona with a population of 25,000. Commitment and selection is dependent upon obtaining and installing a CT scanner. Salary, approximately $80,000, dependent on qualifications. Send CV to Sharon K. Harmeson, Personnel Service, VA Medical Center, Prescott, AZ 86313; or call (602) 445-4860, ext 214. An equal opportunity employer.

(Continued on Page 244)

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ARIZONA

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CIGNA Healthplan
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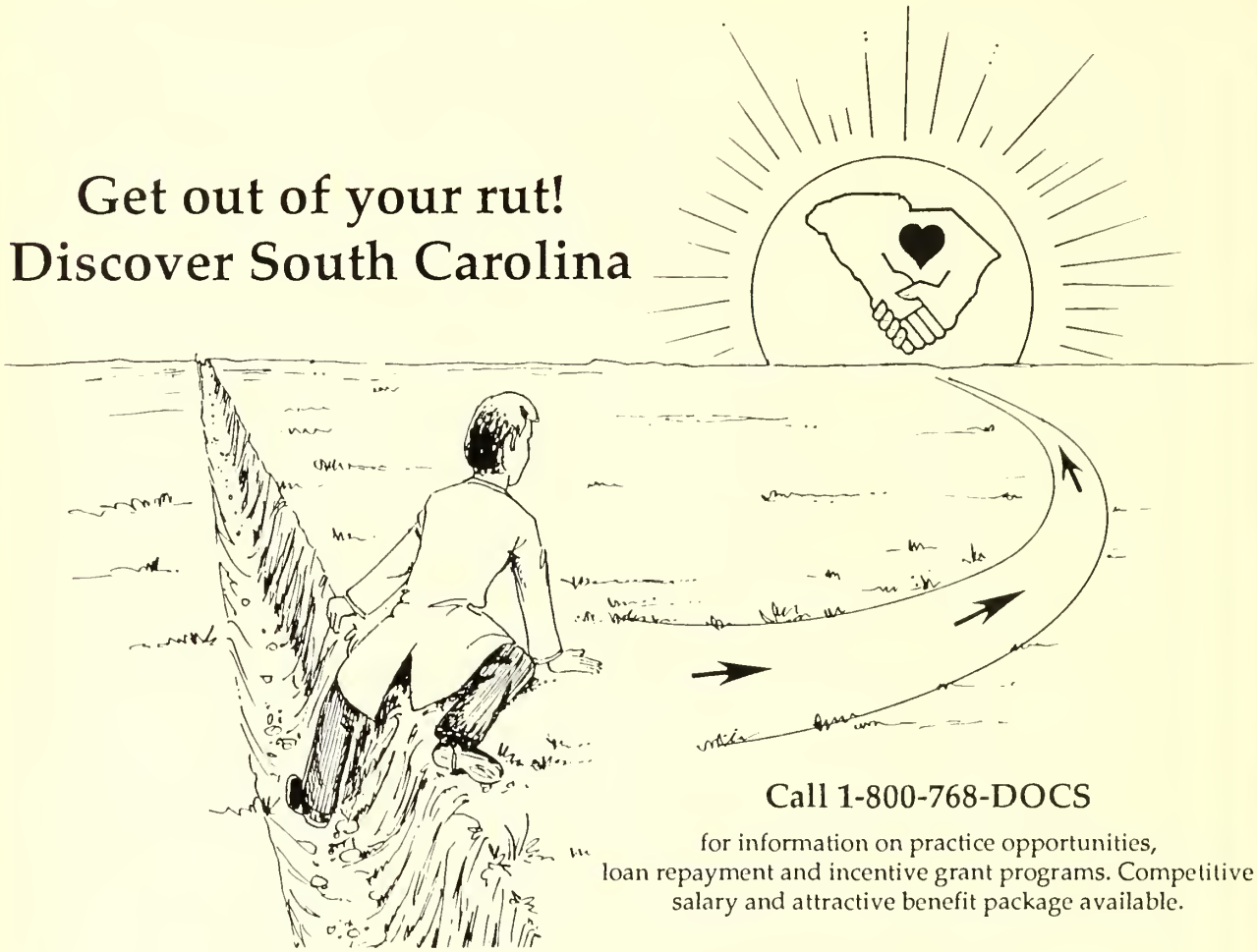

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(Continued from Page 243)

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or send résumé for courteous, confidential consideration to:

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(Continued on Page 245)

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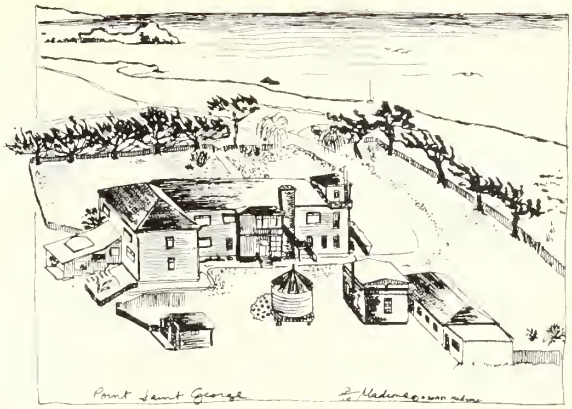

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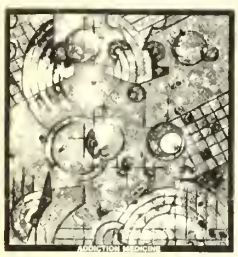

May 1990

A Special Issue of **The Western Journal of Medicine** featuring

- Overview of Addiction Medicine *David Smith, Editor/Founder, Haight-Ashbury Free Clinic*
- Chemical Dependence and Drug Testing in the Workplace *John Osterloh and Charles Becker*
- The New Disease Model of Alcoholism *John Wallace*
- Cognitive Impairment in Abstinent Alcoholics *George Fein, et al*
- Pulmonary Complications of Smoked Substance Abuse *Donald Tashkin*
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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 8-13, 1991, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 20-22, 1991, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-13, 1991, Westin Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-27, 1991, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-4, 1991, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1991, Quail Lodge, Carmel, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-10, 1991, The Marshall Building, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): April 26-28, 1991, Salisham.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 11-13, 1991, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, 1991, Red Lion, Bellevue.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 13-15, 1991, Jackson Lake Lodge, Moran.

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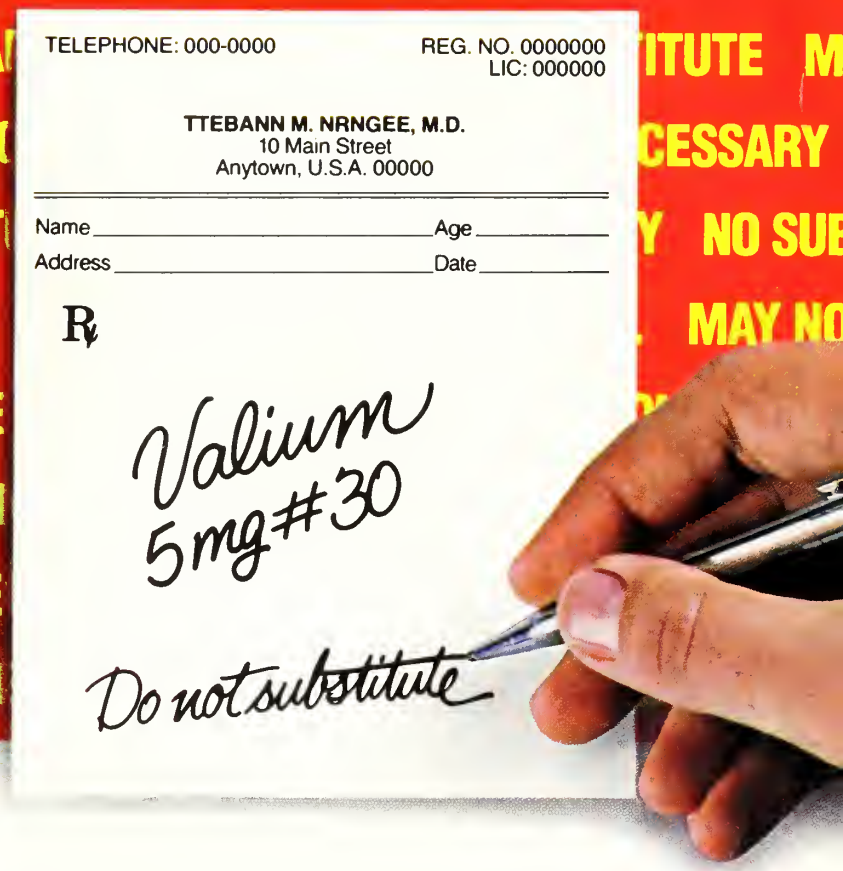

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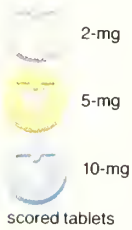

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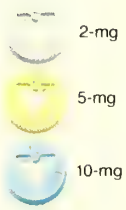

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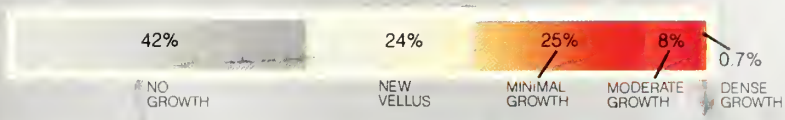

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General Precautions Monitor patients one month after starting ROGAINE and at least every six months afterward Discontinue ROGAINE if systemic effects occur The alcohol base will burn and irritate the eye If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.
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Patient Information A patient information leaflet is included with each package and in the full product information
Drug Interactions No drug interactions are known Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine
Carcinogenesis, Mutagenesis and Impairment of Fertility No carcinogenicity was found with topical application Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice In rats, there was a dose-dependent reduction in conception rate
Pregnancy Category C ROGAINE should not be used by pregnant women
Labor and Delivery The effects are not known
Nursing Mothers ROGAINE should not be administered
Pediatric Use Safety and effectiveness have not been established under age 18

ADVERSE REACTIONS
ROGAINE was used by 3510 patients in placebo-controlled trials Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients
Respiratory (bronchitis, upper respiratory infection, sinusitis) 5 95%, **Dermatologic** (irritant or allergic contact dermatitis) 5 27%, **Gastrointestinal** (diarrhea, nausea, vomiting) 3 42%, **Neurology** (headache, dizziness, faintness, light-headedness) 2 56%, **Musculoskeletal** (fractures, back pain, tendinitis) 2 17%, **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1 28%, **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1 03%, **Special Senses** (conjunctivitis, ear infections, vertigo) 0 94%, **Metabolic-Nutritional** (edema, weight gain) 0 60%, **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0 46%, **Genital Tract** (prostatitis, epididymitis) 0 46%, **Psychiatric** (anxiety, depression, fatigue) 0 28%, **Hematology** (lymphadenopathy, thrombocytopenia) 0 23%, **Endocrine** 0 09%
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions Additional events reported since marketing include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia

DOSAGE AND ADMINISTRATION
Hair and scalp should be dry before application 1 mL should be applied to the total affected areas twice daily Total daily dose should not exceed 2 mL If the fingertips are used to facilitate drug application, wash the hands afterwards

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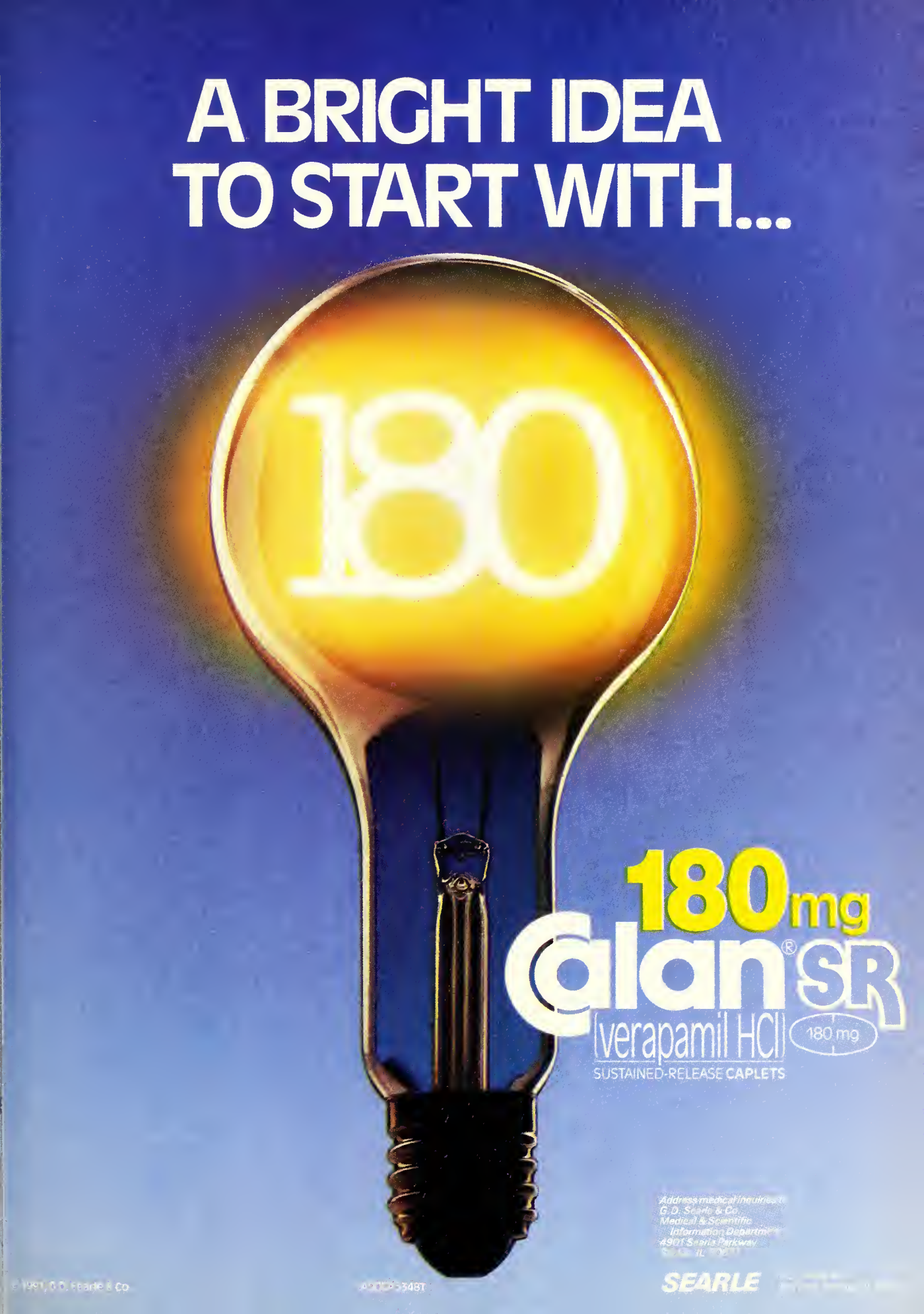
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Dr Bodenheimer is an internist in private practice and Assistant Clinical Professor, University of California, San Francisco, School of Medicine.

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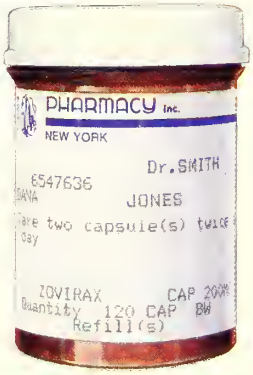

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INDICATIONS AND USAGE. Zovirax Capsules and Suspension are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients

Zovirax Capsules and Suspension are also indicated for the acute treatment of herpes zoster (shingles)

Genital Herpes Infections: The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs Thus orally administered Zovirax is not appropriate in treating all genital herpes infections The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes)

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing The duration of pain and new lesion formation was decreased in some patient groups The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy Patients with mild disease may derive less benefit than those with more severe episodes In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered Zovirax given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively Serial analyses of the 3 month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time

The frequency and severity of episodes of untreated genital herpes may change over time After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects In general, orally administered Zovirax should not be used for the suppression of recurrent disease in mildly affected patients Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease Thus, this regimen should be considered only for appropriate patients with annual re-evaluation

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions

Herpes Zoster Infections: In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to Zovirax and 94 to placebo), Zovirax (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to Zovirax and 43 to placebo), Zovirax (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia)

CONTRAINDICATIONS Zovirax Capsules and Suspension are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations

WARNINGS. Zovirax Capsules and Suspension are intended for oral ingestion only

PRECAUTIONS. **General**: Zovirax has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility) The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION)

Exposure of Herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients The relationship between the *in vitro* sensitivity of Herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY-Microbiology)

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve Urinary excretion and renal clearance were correspondingly reduced The clinical effects of this combination have not been studied

Carcinogenesis, Mutagenesis, Impairment of Fertility The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes) Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics)

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors At 450 mg/kg/day plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay

Acyclovir was tested in two *in vitro* cell transformation assays Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters, higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels) In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels) In all 4 microbial assays, no evidence of mutagenicity was observed Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in man At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels Results in the other five mammalian cell loci follow at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels, at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p o) or in rats (25 mg/kg/day s c) In the mouse study plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels At a higher dose in the rat (50 mg/kg/day s c), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels) No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels) In a rat peri- and postnatal study at 50 mg/kg/day s c (11 to 22 times human levels) there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12 5 mg/kg/day and 25 mg/kg/day, s c The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured) However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels) no drug-related reproductive effects were observed

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy Plasma levels were not measured in the one month study and were 24 to 48 times human levels in the six month study Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day, some evidence of recovery of sperm production was evident 30 days postdose Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels No testicular abnormalities were seen in dogs given 50 mg/kg/day i v for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels)

Pregnancy: ***Teratogenic Effects***. Pregnancy Category C Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p o), rabbit (50 mg/kg/day, s c and i v) or in standard tests in the rat (50 mg/kg/day s c) These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity In this test, rats were given 3 s c doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels There are no adequate and well-controlled studies in pregnant women Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of Zovirax and ranged from 0 6 to 4 1 times corresponding plasma levels These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0 3 mg/kg/day Caution should be exercised when Zovirax is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Herpes Simplex: ***Short-Term Administration***: The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with orally administered Zovirax were nausea and/or vomiting in 8 of 298 patient treatments (2 7%) and headache in 2 of 298 (0 6%) Nausea and/or vomiting occurred in 2 of 287 (0 7%) patients who received placebo

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with orally administered Zovirax (0 3%), included diarrhea, dizziness, anorexia, fatigue, edema skin rash leg pain, inguinal adenopathy, medication taste and sore throat

Long-Term Administration: The most frequent adverse reactions reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 Zovirax - treated patients were nausea (4 8%) diarrhea (2 4%), headache (1 9%) and rash (1 7%) The 589 control patients receiving intermittent treatment of recurrences with Zovirax for 1 year reported diarrhea (2 7%) nausea (2 4%) headache (2 2%) and rash (1 5%)

The most frequent adverse reactions reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1 5%), rash (1 3%) and paresthesia (0 8%) Reactions reported by 329 patients during the third year include asthenia (1 2%) paresthesia (1 2%) and headache (0 9%)

Herpes Zoster The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral Zovirax 5 times daily for 7 to 10 days in 323 patients were malaise (11 5%) nausea (8 0%) headache (5 9%), vomiting (2 5%) diarrhea (1 5%) and constipation (0 9%) The 323 placebo recipients reported malaise (11 1%), nausea (11 5%), headache (11 1%) vomiting (2 5%), diarrhea (0 3%) and constipation (2 4%)

OVERDOSAGE: Precipitation of acyclovir in renal tubules may occur when the solubility (2 5 mg/mL) in the intratubular fluid is exceeded Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species rats treated with i v and i p doses of 20 mg/kg/day for 21 and 31 days, respectively and at s c doses of 100 mg/kg/day for 10 days, rabbits at s c and i v doses of 50 mg/kg/day for 13 days and dogs at i v doses of 100 mg/kg/day for 31 days A 6 hr hemodialysis results in a 60% decrease in plasma acyclovir concentration Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood In the event of acute renal failure and anuria the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION)

DOSAGE AND ADMINISTRATION. **Treatment of initial genital herpes**. 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 10 days

Chronic suppressive therapy for recurrent disease 400 mg (two 200 mg capsules or two teaspoonfuls [10 mL] suspension) 2 times daily for up to 12 months, followed by re-evaluation See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily

Intermittent Therapy: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 5 days Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence

Acute Treatment of Herpes Zoster. 800 mg (four 200 mg capsules or four teaspoonfuls [20 mL] suspension) every 4 hours orally 5 times daily for 7 to 10 days

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications

Normal Dosage Regimen (5x daily)	Creatinine Clearance (mL/min/1 73m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval (hrs)
200 mg every 4 hours	> 10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

For patients who require hemodialysis, the dosing schedule should be adjusted so that a dose is administered after each dialysis

References: 1. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection: a multicenter double-blind trial. *JAMA*. 1988;260:201-206. **2.** Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med*. 1988;85(suppl 2A):14-19. **3.** Data on file, Burroughs Wellcome Co., 1990.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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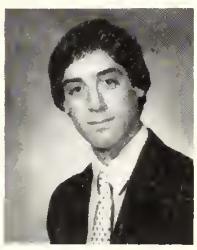
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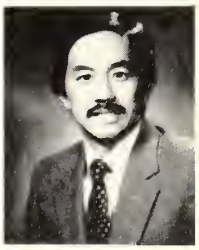
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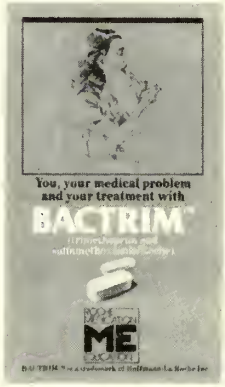

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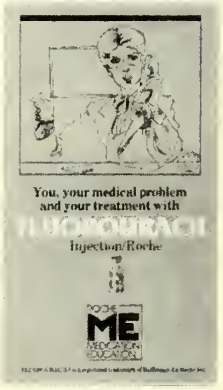

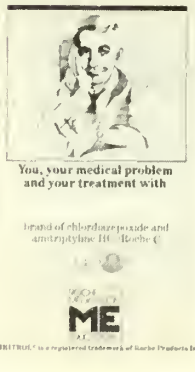

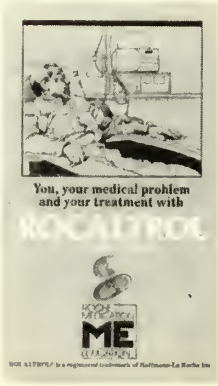

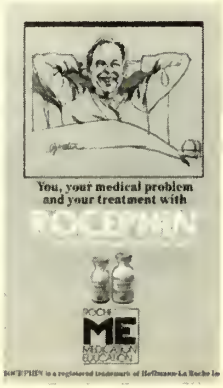

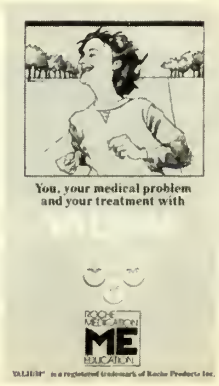

What do breast cancer, hypertension, and HIV infection have in common?

Diagnosis and treatment before symptoms develop can make a difference in a patient's life.

There's more than one way to identify patients at risk of HIV infection.

But the two most important ways are by taking a sexual history and a drug history of all your male and female patients. Asking the right questions in a nonjudgmental way is critical.

A patient's medical history can also hold clues. A history of genital herpes, syphilis, or other STDs may be an indication of at-risk behavior.

You should be aware of lab indicators that signal the possibility of HIV infection: unexplained anemia, increased LDH or serum globulin count, low serum cholesterol count, or idiopathic thrombocytopenic purpura.

And probe for early clinical signs, including recent occurrences of oral thrush, weight loss, perianal herpes, zoster, chronic vaginitis, and hairy leukoplakia.

Once you suspect HIV infection, testing can make a difference.

Just as you would suggest mammography for patients at risk of breast cancer, suggest HIV testing once you've identified patients at risk of infection.

Because today, early, aggressive treatments can make a difference in the lives of patients who test positive.

Early treatment with RETROVIR helps keep asymptomatic patients symptom-free longer.

Now, treatments are available that can alter the course of HIV disease, especially when begun early–including treatment with RETROVIR.

RETROVIR Reduces the Rate of HIV Disease Progression by More Than Half[1]

	Placebo†	RETROVIR†
Progressions to AIDS*	33 6.6 rate‡	11 2.3 rate‡

*Patients were monitored for an average of one year.
†RETROVIR: n=453; placebo: n=428. Dosage was 500 mg/day.
‡Events per 100 person-years of observation.

In a recent study of asymptomatic patients (CD4 ≤500 cells/mm³), RETROVIR reduced the rate of disease progression by more than half, at a dosage of 500 mg/day. Patients stayed symptom-free longer with RETROVIR.[1]

Although treatment of asymptomatic patients keeps them symptom-free longer and delays progression of disease, it is not known whether early treatment prolongs survival. RETROVIR has been studied in controlled trials in significant numbers of patients for limited periods of time. Therefore, the full safety and efficacy profile of RETROVIR has not yet been defined.

ETROVIR at 500 mg/day is ell tolerated.

RETROVIR at the dose of 500 mg/day in mptomatic patients is generally well tolerated.[1] e occurrence of serious adverse events, compared h that initially reported with the higher doses of TROVIR in advanced ARC/AIDS patients, has en greatly reduced.

So start probing early for HIV infection in your ctice. Diagnosis and treatment can make a ference in your patients' lives.

ference: 1. Volberding PA, Lagakos SW, Koch MA, et al. lovudine in asymptomatic human immunodeficiency s infection: a controlled trial in persons with fewer than CD4-positive cells per cubic millimeter. *N Engl J Med.* 0;322:941-949.

Now more than ever– est, monitor, and, hen appropriate, treat.

RETROVIR®
(zidovudine)
CAPSULES AND SYRUP

LIVING WITH HIV.

See following pages for brief summary of prescribing information.

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(ZIDOVUDINE)

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BRIEF SUMMARY

WARNING: THERAPY WITH RETROVIR (ZIDOVUDINE) MAY BE ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING GRANULOCYTOPENIA AND SEVERE ANEMIA REQUIRING TRANSFUSIONS (SEE WARNINGS)

IN ADDITION, PATIENTS TREATED WITH ZIDOVUDINE MAY CONTINUE TO DEVELOP OPPORTUNISTIC INFECTIONS (OI'S) AND OTHER COMPLICATIONS OF HIV INFECTION AND, THEREFORE SHOULD BE UNDER CLOSE CLINICAL OBSERVATION

Microbiology: The development of resistance to zidovudine has not been adequately studied and the frequency of zidovudine-resistant isolates existing in the general population is unknown. Reduced *in vitro* sensitivity to zidovudine has been observed, however, in viral isolates from some individuals who have received prolonged courses of zidovudine treatment. For the small number of patients from whom isolates were studied, no correlations were evident between the development of reduced sensitivity in the laboratory and clinical response. Therefore, the quantitative relationship between *in vitro* susceptibility of HIV to zidovudine and clinical response to therapy has not been established. Studies of the development of resistance to zidovudine are incomplete and the frequency and degree of changes in *in vitro* sensitivity of virus isolates from HIV infected patients with differing severity of immune compromise are unknown.

INDICATIONS AND USAGE: Retrovir is indicated for the management of adult patients with HIV infection who have evidence of impaired immunity (CD4 cell count of 500/mm³ or less) before therapy is begun. Retrovir is also indicated for HIV-infected children over 3 months of age who have HIV-related symptoms or who are asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression.

These indications are based on the results of three randomized, double-blind, placebo-controlled trials of oral zidovudine in HIV-infected adult patients with CD4 cell counts of 500/mm³ or less, and two open-label studies involving 124 children ages 3 months to 12 years with advanced HIV-associated disease. Specifically, separate studies evaluated zidovudine therapy in asymptomatic HIV-infected adults, in adults with early symptomatic disease, in adults with advanced symptomatic HIV disease (AIDS or advanced ARC), and in children with advanced symptomatic HIV disease (pediatric AIDS or advanced ARC).

Adults Asymptomatic HIV Infection: A randomized, double-blind, placebo-controlled trial of oral zidovudine was conducted in asymptomatic, HIV-infected adults at 32 medical centers. Entry was dependent on the absence of signs and symptoms consistent with HIV disease, such as significant weight loss, fever, diarrhea, secondary infections and evidence of neurological dysfunction. In the study, 1338 asymptomatic individuals with absolute CD4(T4) lymphocyte counts of less than 500 cells/mm³ received a regimen of either 100 mg zidovudine, 300 mg zidovudine, or placebo, each administered five times a day. These study participants were monitored for the development of signs and symptoms of HIV disease and tolerance to the study regimens. The study was terminated early because of a statistically significant difference in progression to advanced symptomatic HIV disease (AIDS or advanced ARC) between the 500 mg/day zidovudine group and the placebo group. Of the 1338 patients enrolled in the study, 38 of the 428 patients receiving placebo, 17 of the 453 individuals receiving 500 mg zidovudine, and 19 of the 457 recipients of 1500 mg zidovudine progressed to advanced symptomatic HIV disease when followed for a mean of 55 weeks (range 19-107 weeks). Of the progressions noted above, AIDS occurred in 33 placebo recipients, 11 individuals receiving 500 mg and 14 patients receiving 1500 mg zidovudine. Changes in immunologic and virologic parameters (ie, CD4[T4] lymphocyte count and serum p24 antigen levels) paralleled the observed clinical benefits. Consistent with various epidemiologic studies of individuals with HIV infection, patients in this study with lower CD_4 cell counts or P24 antigenemia were more likely to progress to AIDS. Virtually all patients (for whom data are available) experienced a decline in CD_4 cell counts to less than 200 per mm³ before developing an AIDS-defining opportunistic infection. Although treatment of asymptomatic patients delays progression of disease in those patients at risk of progression over the initial 1-2 years of treatment, it is not known whether early treatment prolongs survival.

Zidovudine was well tolerated in a majority of patients. The following adverse clinical events were reported at a significantly greater incidence in individuals receiving 500 mg/day of zidovudine versus placebo: headache, malaise, anorexia, nausea and vomiting (see ADVERSE REACTIONS).

The two most common laboratory abnormalities reported were anemia and granulocytopenia, each of which occurred more often in patients receiving higher doses. These toxicities were easily managed in most cases by temporary dose interruption.

Early Symptomatic HIV Disease: This randomized, double-blind, placebo-controlled trial of oral zidovudine, conducted at 29 medical centers, studied 713 adults with early manifestations of HIV disease (ie, a baseline CD4[T4] cell count of 200 to 800/mm³ and symptoms such as oral thrush, oral hairy leukoplakia or intermittent diarrhea). Patients received either placebo or 200 mg zidovudine every 4 hours (1200 mg/day). The trial was terminated early because of a statistically significant difference in the rates of development of advanced symptomatic HIV disease between the zidovudine and placebo groups. Of the 352 patients receiving placebo, 36 progressed to advanced symptomatic HIV disease, of whom 21 progressed to AIDS, whereas of the 361 zidovudine recipients, 13 progressed to advanced symptomatic HIV disease, of whom 5 progressed to AIDS.

Minimal toxicity was observed. Four percent of zidovudine recipients compared with none of the placebo recipients developed a hemoglobin concentration less than 8 g/dL and 4% of patients treated with zidovudine compared with 1% of placebo recipients developed a granulocyte count less than 750 cells/mm³. Asthenia, dyspepsia, nausea, and vomiting were the major adverse clinical events reported at significantly greater incidences in patients receiving zidovudine.

Advanced Symptomatic HIV Disease: This randomized, double-blind, placebo-controlled trial, conducted at 12 medical centers, was the original trial upon which the marketing of Retrovir was based. In this trial, 281 adults with advanced symptomatic HIV infection including AIDS were studied for a mean of four and a half months.

The patient population of this controlled trial consisted of 160 patients with AIDS (85 Retrovir and 75 placebo) who had recovered from their first episode of PCP diagnosed within the previous four months and 121 patients with ARC (59 Retrovir and 62 placebo) with multiple signs and symptoms of HIV infection, including mucocutaneous candidiasis and/or unexplained weight loss (≥ 15 lbs or >10% of prior body weight). All patients had evidence of impaired cellular immunity with an absence of delayed cutaneous hypersensitivity and CD4 (T4) lymphocytes less than 500 cells/mm³. All patients began therapy at a dose of 250 mg every 4 hours around the clock. This dosage was reduced or temporarily or permanently discontinued after serious marrow toxicity occurred. The trial was stopped early because of a statistically significant difference in mortality. There were 19 deaths in the placebo group and 1 in the Retrovir group. All deaths were apparently due to opportunistic infections (OI) or other complications of HIV infection. Treatment duration ranged from 12 weeks to 26 weeks, with a mean and median duration of 17 and 18 weeks, respectively.

Retrovir also significantly reduced the risk of acquiring an AIDS-defining OI in patients after 6 weeks of treatment. In addition, patients who received Retrovir generally did better than the placebo group in terms of several other measures of efficacy including performance level, neuropsychiatric function, maintenance of body weight and the number and severity of symptoms associated with HIV infection. A small, transient increase in mean CD4 (T4) counts was seen in the zidovudine group but the significance of this finding is unclear.

The most significant adverse reaction noted in the study was a depression of formed elements in the peripheral blood, which necessitated dose reduction or drug discontinuation in 34% of patients receiving Retrovir. Patients with lower CD4 counts were more likely to receive transfusions: 41% of Retrovir recipients and 16% of placebo recipients with <200 CD4 lymphocytes at entry were transfused (see ADVERSE REACTIONS). Only one of 30 Retrovir recipients and none of 30 placebo recipients with >200 CD4 lymphocytes required transfusion.

Although mean platelet counts in Retrovir recipients were statistically increased compared to mean baseline values, thrombocytopenia did occur in some patients. Twelve percent (12%) of Retrovir recipients compared to 5% of placebo recipients had >50% decreases from baseline platelet count.

At the conclusion of the placebo-controlled trial, approximately 80% of Retrovir and placebo recipients elected to enroll in an uncontrolled extension protocol in which all patients received Retrovir at a dose of 200 mg every four hours. This dose was chosen because of concern about hematologic toxicity and to allow for greater flexibility in dosing. These patients have been followed for variable periods of time. As the follow-up period lengthened, patient tracking became increasingly difficult. The intended treatment period of the original study was six months, however, some follow-up data are available for over 90% of patients originally enrolled in the trial. Data from patients in this and other studies show no new or unexpected clinical or laboratory adverse experiences for patients receiving Retrovir other than those listed (see ADVERSE REACTIONS), nor have previously reported adverse events increased significantly in frequency or severity with prolonged drug administration. At any time on study, approximately half of the patients received the recommended dose of zidovudine, while the remaining patients required reduction or interruption of their dosage regimen in response to myelosuppression and/or other clinical adverse events.

Benefits of therapy with Retrovir were observed during this extended period, although opportunistic infections continued to occur and additional patients died. Survival for all patients originally randomized to receive Retrovir was 96.5% at six months, 84.7% at one year, 68.3% at 18 months and 41.2% at two years. One year and two year survival for patients who entered the trial with AIDS was 79% and 31% when calculated since initiation of therapy (87% and 43%, respectively, since the first diagnosis of PCP). These survival rates were determined by the "intention to treat" method, which assumes all patients assigned to a drug actually took the drug throughout the study period.

While a direct comparison with survival data from other cohorts is not possible, untreated adult patients with AIDS diagnosed in San Francisco in 1985 who had survived 60 days after PCP had a one year survival of 34.7% and a two year survival of 4.2% from diagnosis of PCP. In a recent epidemiologic study of patients with AIDS diagnosed in San Francisco in 1986 and 1987, median survival was improved for patients receiving Retrovir compared to those not receiving therapy with Retrovir (21.6 vs 14.9 months). Actual survival of untreated patients is likely to be lower than reported because of the difficulty in complete ascertainment of mortality. Caution is advised in making comparisons from such "natural history" experience since case definitions and follow-up practices vary.

Other, uncontrolled studies have shown that Retrovir may be of benefit in treating women, intravenous drug users, and racial minorities, in addition to the patient population (primarily white males) included in the controlled trials.

Dose Comparison Study: Results from a randomized, unblinded, dose comparison study of zidovudine in adults with AIDS who had experienced an episode of PCP, indicate that an induction dose of zidovudine 200 mg administered orally every four hours (1200 mg/day) for one month, followed by chronic administration of 100 mg every 4 hours (600 mg/day), was associated with survival rates and frequency of opportunistic infections comparable to those observed in patients administered higher dosages as tolerated. The 600 mg per day regimen was also associated with a lower incidence of hematologic toxicity. The effectiveness of this lower dose in improving the neurologic dysfunction associated with HIV disease, however, is unknown (see DOSAGE AND ADMINISTRATION).

Pediatric Symptomatic HIV Disease: Two open-label studies have evaluated the pharmacokinetics, safety and efficacy of Retrovir in 124 children with advanced HIV disease (84 AIDS and 40 with other clinical and laboratory evidence of advanced HIV disease). The median age at entry was 3.3 years with 14% less than 12 months of age. In the majority of cases (73%), HIV was acquired by vertical transmission from an HIV-infected mother.

Thirty-six children were enrolled in the Phase 1 study, which evaluated three intravenous dosing regimens administered for 4 to 8 weeks. All children subsequently switched to an oral dose of 180 mg/m² every 6 hours and were followed for a mean of 465 days (range 121 to 855 days). Eighty-eight children participated in the Phase 2 study and these children were monitored for a mean of 186 days (range 3 to 352 days). In the Phase 2 study, oral zidovudine was initiated at a dose of 180 mg/m² every 6 hours.

Clinical, immunologic and virologic improvements were observed among some of the children receiving zidovudine in these open-label studies. Clinical improvements included reductions in hepatosplenomegaly and increases in weight percentiles in previously growth retarded children. The probability of remaining free of opportunistic infections through 12 months of follow-up was 0.76. Thirty-seven children developed one or more documented serious bacterial infections while participating in the studies. Seven of these children had more than one documented serious bacterial infection. The probability of survival at 12 months is 0.87 for the 124 patients enrolled in the Phase 1 and Phase 2 studies.

Improvements in the immunologic parameters CD4 cell counts and immunoglobulin concentration were observed among the study participants. For children with severely depressed CD4 cell counts (<500/mm³) at entry, a mean increase of 148/mm³ in CD4+ lymphocyte cell count was observed during the first two months of zidovudine therapy. Thereafter, CD4 cell counts declined but remained above baseline through 9 months of follow-up. A tendency towards normalization of elevated immunoglobulin concentrations (primarily IgG) was observed among study participants.

Substantial reductions in serum and CSF P_{24} antigen concentrations were observed in some patients, as well as a reduction in the number of patients with positive CSF HIV cultures, providing evidence of anti-retroviral effect.

The most frequently reported adverse events were anemia (Hgb < 7.5 g/dL) and neutropenia (< 750/mm³), which occurred in forty-six percent of the children. Thirty-six percent of the patients had their dose modified due to the development of hematologic abnormalities and 30% received transfusions for anemia. Four patients had dosing permanently discontinued due to neutropenia (see ADVERSE REACTIONS).

CONTRAINDICATIONS: Retrovir Capsules and Syrup are contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulations.

WARNINGS: Zidovudine has been studied in controlled trials in significant numbers of asymptomatic and symptomatic HIV infected patients, but only for limited periods of time. Therefore, the full safety and efficacy profile of zidovudine has not been defined, particularly in regard to prolonged use and especially in HIV infected individuals who have less advanced disease (see following sections for more specific information: INDICATIONS AND USAGE, Microbiology, Carcinogenesis, Mutagenesis, Impairment of Fertility).

Insufficient clinical experience exists to recommend a dosing regimen in infants under 3 months of age. Preliminary evidence indicates that zidovudine clearance may be reduced in children less than one month of age.

A positive test for HIV-antibody in children under 15 months of age may represent passively acquired maternal antibodies, rather than an active antibody response to infection in the infant. Thus, the presence of HIV antibody in a child less than 15 months of age must be interpreted with caution, especially in the asymptomatic infant. Confirmatory tests such as serum P_{24} antigen or viral culture should be pursued in such children.

Zidovudine should be used with extreme caution in patients who have bone marrow compromise evidenced by granulocyte count <1000/mm³ or hemoglobin <9.5 g/dL. In all of the placebo-controlled studies, but most frequently in patients with advanced symptomatic HIV disease, anemia and granulocytopenia were the most significant adverse events observed (see ADVERSE REACTIONS). There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuance of the drug.

Significant anemia most commonly occurred after 4 to 6 weeks of therapy and in many cases required dose adjustment, discontinuation of zidovudine, and/or blood transfusions. Frequent blood counts are strongly recommended in patients with advanced HIV disease taking zidovudine. For asymptomatic HIV-infected individuals and patients with early HIV disease, most of whom have better marrow reserve, blood counts may be obtained less frequently, depending upon the patient's overall status. If anemia or granulocytopenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION in full prescribing information).

Sensitization reactions, including anaphylaxis in one patient, have been reported in individuals receiving zidovudine therapy. Patients experiencing a rash should undergo medical evaluation.

Coadministration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the toxicity of either drug may be potentiated (see Drug Interactions under PRECAUTIONS). Zidovudine recipients who used acetaminophen during the controlled trial in advanced HIV disease, had an increased incidence of granulocytopenia which appeared to be correlated with the duration of acetaminophen use.

PRECAUTIONS:

General: Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). There are currently very little data available concerning the use of zidovudine in patients with impaired renal function (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY) and no data in patients with impaired hepatic function. These patients may be at greater risk of toxicity from zidovudine.

Information for Patients: See full prescribing information.

Drug Interactions: The interaction of other drugs with zidovudine has not been studied in a systematic manner. Coadministration of zidovudine with drugs that are nephrotoxic, cytotoxic, or which interfere with RBC/WBC number or function (eg, dapsone, pentamidine, amphotericin B, flucytosine, vincristine, vinblastine, adriamycin, or interferon) may increase the risk of toxicity. Limited data suggest that probenecid may inhibit glucuronidation and/or reduce renal excretion of zidovudine. In addition, other drugs (eg, acetaminophen, aspirin, or indomethacin) may competitively inhibit glucuronidation (see WARNINGS). Phenytoin levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. These observations suggest that phenytoin levels should be carefully monitored in patients receiving zidovudine since many patients with advanced HIV infections have CNS conditions which may predispose to seizure activity.

Some experimental nucleoside analogues which are being evaluated in HIV-infected patients may affect RBC/WBC number or function and may increase the potential for hematologic toxicity of zidovudine. Some experimental nucleoside analogues affecting DNA replication antagonize the *in vitro* antiviral activity of zidovudine against HIV and thus, concomitant use of such drugs should be avoided.

Some drugs such as trimethoprim-sulfamethoxazole, pyrimethamine, and acyclovir may be necessary for the management or prevention of opportunistic infections. In the controlled trial, in patients with advanced HIV disease, increased toxicity was not detected with limited exposure to these drugs. However, there is one published report of neurotoxicity (profound lethargy) associated with concomitant use of zidovudine and acyclovir.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Zidovudine was administered orally at three dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60 and 120 mg/kg/day in mice and 80, 220 and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30 and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, seven late-appearing (after 19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, one squamous cell papilloma and one squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle dose animal. No vaginal tumors were found at the lowest dose.

In rats, two late-appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats.

No other drug-related tumors were observed in either sex of either species.

It is not known how predictive the results of rodent carcinogenicity studies may be for man. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

No evidence of mutagenicity (with or without metabolic activation) was observed in the Ames *Salmonella* mutagenicity assay. In a mutagenicity assay conducted in L5178Y/TK+/- mouse lymphoma cells, zidovudine

RETROVIR® (ZIDOVUDINE) Capsules and Syrup

was weakly mutagenic in the absence of metabolic activation only at the highest concentrations tested (4000 and 5000 μg/mL). In the presence of metabolic activation, the drug was weakly mutagenic at concentrations of 1000 μg/mL and higher. In an *in vitro* mammalian cell transformation assay, zidovudine was positive at concentrations of 0.5 μg/mL and higher. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities at concentrations of 3 μg/mL and higher. No such effects were noted at the two lowest concentrations tested. 0.3 and 1 μg/mL. In an *in vivo* cytogenetic study in rats given a single intravenous injection of zidovudine at doses of 37.5 to 300 mg/kg, there were no treatment-related structural or numerical chromosomal alterations in spite of plasma levels that were as high as 453 μg/mL five minutes after dosing.

In two *in vivo* micronucleus studies (designed to measure chromosome breakage or mitotic spindle apparatus damage) in male mice, oral doses of zidovudine of 100 to 1000 mg/kg/day administered once daily for approximately 4 weeks induced dose-related increases in micronucleated erythrocytes. Similar results were also seen after 4 or 7 days of dosing at 500 mg/kg/day in rats and mice.

No effect on male or female fertility (judged by conception rates) was seen in rats given zidovudine orally at doses up to 450 mg/kg/day.

Pregnancy: Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. The incidence of fetal resorptions was increased in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak plasma concentrations in rats of 68 to 234 times the peak human plasma concentrations and in rabbits of 14 to 90 times the peak human plasma concentrations. It is not known whether zidovudine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Zidovudine should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether zidovudine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from zidovudine in nursing infants, mothers should be instructed to discontinue nursing if they are receiving zidovudine.

Pediatric Use: See INDICATIONS and WARNINGS sections.

ADVERSE REACTIONS. **Adults**: The frequency and severity of adverse events associated with the use of zidovudine in adults are greater in patients with more advanced infection at the time of initiation of therapy. The following tables summarize the relative incidence of hematologic adverse events observed in the placebo-controlled clinical studies by severity of HIV disease present at the start of treatment.

Asymptomatic HIV Infection Study (n=1338)	Granulocytopenia (<750/mm³)		
	Zidovudine		Placebo
	1500 mg*	500 mg	
CD4 ≤ 500	6.4% (n=457)	1.8% (n=453)	1.6% (n=428)
Asymptomatic HIV Infection Study (n=1338)	**Anemia (Hgb<8 g/dL)**		
	Zidovudine		Placebo
	1500 mg*	500 mg	
CD4 ≤ 500	6.4% (n=457)	1.1% (n=453)	0.2% (n=428)

Early Symptomatic HIV Disease Study (n=713)	Granulocytopenia (<750/mm³)		Anemia (Hgb<8 g/dL)	
	Zidovudine 1200 mg	Placebo	Zidovudine 1200 mg	Placebo
CD4>200	4%(n=361)	1%(n=352)	4%(n=361)	0%(n=352)

Advanced Symptomatic HIV Disease Study (n=281)	Granulocytopenia (<750/mm³)		Anemia (Hgb<7.5 g/dL)	
	Zidovudine 1500 mg*	Placebo	Zidovudine 1500 mg*	Placebo
CD4>200	10%(n=30)	3%(n=30)	3%(n=30)	0%(n=30)
CD4<200	47%(n=114)	10%(n=107)	29%(n=114)	5%(n=107)

*Three times the currently recommended dose in asymptomatic patients.

The anemia reported in patients receiving zidovudine appeared to be the result of impaired erythrocyte maturation as evidenced by increased macrocytosis (MCV) while on drug.

The HIV-infected adults participating in these clinical trials often had baseline symptoms and signs of HIV disease and/or experienced adverse events at some time during study. It was often difficult to distinguish adverse events possibly associated with zidovudine administration from underlying signs of HIV disease or intercurrent illnesses. The following table summarizes clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with zidovudine in the original placebo-controlled study. Of the items listed in the table, only severe headache, nausea, insomnia and myalgia were reported at a significantly greater rate in zidovudine recipients.

Percentage (%) of Patients with Clinical Events in the Advanced HIV Disease Study		
Adverse Event	Zidovudine (n=144) %	Placebo (n=137) %
BODY AS A WHOLE		
Asthenia	19	18
Diaphoresis	5	4
Fever	16	12
Headache	42	37
Malaise	8	7
GASTROINTESTINAL		
Anorexia	11	8
Diarrhea	12	18
Dyspepsia	5	4
GI Pain	20	19
Nausea	46	18
Vomiting	6	3
MUSCULOSKELETAL		
Myalgia	8	2
NERVOUS		
Dizziness	6	4
Insomnia	5	1
Paresthesia	6	3
Somnolence	8	9
RESPIRATORY		
Dyspnea	5	3
SKIN		
Rash	17	15
SPECIAL SENSES		
Taste Perversion	5	8

Clinical adverse events which occurred in less than 5% of all adult patients treated with zidovudine in the advanced HIV study are listed below. Since many of these adverse events were seen in placebo-treated patients as well as zidovudine recipients, their possible relationship to the drug is unknown.

Body as a whole: body odor, chills, edema of the lip, flu syndrome, hyperalgesia, back pain, chest pain, lymphadenopathy

Cardiovascular: vasodilation

Gastrointestinal: constipation, dysphagia, edema of the tongue, eructation, flatulence, bleeding gums, rectal hemorrhage, mouth ulcer

Musculoskeletal: arthralgia, muscle spasm, tremor, twitch

Nervous: anxiety, confusion, depression, emotional lability, nervousness, syncope, loss of mental acuity, vertigo

Respiratory: cough, epistaxis, pharyngitis, rhinitis, sinusitis, hoarseness

Skin: acne, pruritus, urticaria

Special senses: amblyopia, hearing loss, photophobia

Urogenital: dysuria, polyuria, urinary frequency, urinary hesitancy

Subsequent to the initial trial, myopathy and sensitization reactions, including anaphylaxis in one patient, have been reported in adults receiving zidovudine therapy.

All unexpected events and expected events of a severe or life-threatening nature were monitored for adults in the placebo-controlled studies in early HIV disease and asymptomatic HIV infection. Data concerning the occurrence of additional signs or symptoms were also collected. No distinction was made in reporting events between those possibly associated with the administration of the study medication and those due to the underlying disease. The following tables summarize all those events reported at a statistically significant greater incidence for zidovudine recipients in these studies.

Percentage (%) of Patients with Clinical Events in the Early Symptomatic HIV Disease Study		
Adverse Event	Zidovudine (n=361) %	Placebo (n=352) %
BODY AS A WHOLE		
Asthenia	69	62
GASTROINTESTINAL		
Dyspepsia	6	1
Nausea	61	41
Vomiting	25	13

Percentage (%) of Patients with Clinical Events* in an Asymptomatic HIV Infection Study			
Adverse Event	1500 mg Zidovudine*** (n=457) %	500 mg Zidovudine (n=453) %	Placebo (n=428) %
BODY AS A WHOLE			
Asthenia	10.1	8.6**	5.8
Headache	58.0**	62.5	52.6
Malaise	55.6	53.2	44.9
GASTROINTESTINAL			
Anorexia	19.3	20.1	10.5
Constipation	8.1	6.4**	3.5
Nausea	57.3	51.4	29.9
Vomiting	16.4	17.2	9.8
NERVOUS			
Dizziness	20.8	17.9**	15.2

*Reported in ≥5% of study population

**Not statistically significant versus placebo

***Three times the currently recommended dose in asymptomatic patients

The following events have been reported in adult patients treated with zidovudine: seizures, nail pigmentation, changes in liver function tests. They may also occur as part of the underlying disease process. As such, the relationship between these events and the use of zidovudine is uncertain.

Pediatrics: The incidences of anemia and granulocytopenia among children with advanced HIV disease receiving zidovudine were similar to the incidences which have been reported for adults with AIDS or advanced ARC (see above). Management of neutropenia and anemia included, in some cases, dose modification and/or blood product transfusions. In the open-label studies, seventeen percent had their dose modified (generally a reduction in dose by 30%) due to anemia and 25% had their dose modified (temporary discontinuation or dose reduction by 30%) for neutropenia. Four children had zidovudine permanently discontinued for neutropenia. The following table summarizes the occurrence of anemia (Hgb < 7.5 g/dL) and granulocytopenia (<750/mm³) among 124 children receiving zidovudine for a mean of 267 days (range 3 to 855 days).

Advanced Pediatric HIV disease (N=124)	Granulocytopenia (< 750/mm³)		Anemia (Hgb < 7.5 g/dL)	
	N	%	N	%
	48	39	28*	23

*Twenty-two children received one or more transfusions due to a decline in hemoglobin to < 7.5 g/dL; an additional 15 children were transfused for hemoglobin levels > 7.5 g/dL. Fifty-nine percent of the patients transfused had a pre-study history of anemia or transfusion requirement.

An increase in MCV (macrocytosis) was observed among the majority of children enrolled in the studies.

In the open-label studies involving 124 children, 16 clinical adverse events were reported by 24 children. No event was reported by more than 5.6% of the study populations. Due to the open-label design of the studies, it was difficult to determine possible zidovudine-related versus disease-related events. Therefore, all clinical events reported as associated with zidovudine therapy or of unknown relationship to zidovudine therapy are presented in the following table.

Percentage (%) of Pediatric Patients with Clinical Events in Open Label Studies		
Adverse Event	N	%
BODY AS A WHOLE		
Fever	4	3.2
Phlebitis*/Bacteremia	2	1.6
Headache	2	1.6
GASTROINTESTINAL		
Nausea	1	0.8
Vomiting	6	4.8
Abdominal Pain	4	3.2
Diarrhea	1	0.8
Weight Loss	1	0.8
NERVOUS		
Insomnia	3	2.4
Nervousness/Irritability	2	1.6
Decreased Reflexes	7	5.6
Seizure	1	0.8
CARDIOVASCULAR		
Left Ventricular Dilation	1	0.8
Cardiomyopathy	1	0.8
S_3 Gallop	1	0.8
Congestive Heart Failure	1	0.8
Generalized Edema	1	0.8
ECG Abnormality	3	2.4
UROGENITAL		
Hematuria/Viral Cystitis	1	0.8

*Peripheral vein I.V. catheter site

The clinical adverse events reported among adult zidovudine recipients may also occur in children.

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ALASKA

The listing of continuing medical education programs in Alaska is supplied by the Alaska State Medical Association. To list programs, please send information to Alaska State Medical Association, 4107 Laurel St, Anchorage 99508; or phone (907) 562-2662.

April 24-27—**Alaska State Medical Association Annual Meeting.** Juneau. Wed-Sat. Contact: Alaska State Medical Association, 4107 Laurel St, Anchorage 99508. (907) 562-2662.

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 15-16—**Ophthalmology Spring Symposium.** U of A, Tucson. Mon-Tues. Contact: Anita Russell, (602) 626-7832.

March 16-20—**Fifth Annual Magnetic Resonance Imaging Conference.** Barrow Neurological Institute at Marriott's Camelback Inn, Scottsdale. Sat-Wed. Contact: Kevin King, RT, (602) 285-3956.

March 24-27—**Management Strategies in Complex Congenital Heart Disease.** Mayo Clinic, Rochester, Minn, at Marriott's Camelback Inn, Scottsdale. Sun-Wed. Contact: Bonita Walin, (800) 323-2688.

April 9-12—**Primary Care Update.** U of A, Tucson. Tues-Fri. Contact: Debbie Stymore, (602) 626-7736.

April 25-26—**Clinical Reviews 1991.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

April 27—**Gastroenterology: Update for the Family Practitioner.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Sat. Contact: Mayo-Clinic Scottsdale.

April 27—**Urology for the Primary Care Physician.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

March 23-24—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Newport Beach Marriott. Sat-Sun. 9 hrs. $150. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 16-19—**California Society of Anesthesiologists Annual Meeting.** CSA at Marriott Hotel, Anaheim. Thurs-Sun. 20 hrs. $175. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

September 7-8—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Horizon Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, Ste 410, Foster City. (800) 345-3691.

CARDIOLOGY

March 22-23—**Coronary Heart Disease Update.** Medical Education Resources at Hyatt Regency Alicante, Anaheim. Fri-Sat. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051

(Continued on Page 272)

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(Continued from Page 270)

April 2-4—**1st Annual Symposium of Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. $750. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 19-20—**Cardiac Diagnostic Methods and Risk Management.** Medical Education Resources at San Diego Hilton. Fri-Sat. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

April 22-May 1—**Cardiology for the Consultant: A Physician's Retreat.** Scripps Clinic and Research Foundation at Inn Rancho Santa Fe. 1½ wks. Contact: Mary Ann Morris, 860 SW Scherer Rd, Lee's Summit, MO 64063. (816) 524-5780.

June 21-22—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 1-3—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

August 2-4—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Hotel, Monterey. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 16-18—**Cardiac Diagnostic Methods and Risk Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

May 18-19—**Advanced Dermatologic Surgery Workshop.** UCLA at the Westwood Marquis Hotel, Westwood. Sat-Sun. 15 hrs. $800. Contact: UCLA.

July 19-21—**Contact Dermatitis: The Basics.** Stanford at Hotel Meridien, San Francisco. Fri-Sun. Contact: Pamela Bain, Dept of Dermatology, Room R-122, Stanford 94305. (415) 723-7854.

August 16-20—**Fifth Annual Hot Spots in Dermatology: Masters Under the Mango Trees.** The Hawaii Dermatology Society and the Kauai Foundation at the Kaluakoi Hotel, Kepuhi Beach, Molokai, Hawaii. Fri-Tues. Contact: David Elpern, MD, Box 457, Kalaheo, HI 96741. (808) 245-1505.

EMERGENCY MEDICINE

March 18-22—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $485. Contact: UCSD.

April 3-6—**Advances in Emergency Medicine.** UCSF at Sheraton Palace Hotel. San Francisco. Wed-Sat. 22 hrs. $435. Contact: UCSF.

April 5-6—**Advantages in Emergency Medicine: Toxicology and Infectious Disease.** UCLA at Hotel del Coronado, Coronado. Fri-Sat. 16 hrs. $95. Contact: UCLA.

April 13—**Critical Care Medicine.** Grossmont Hospital at San Diego Convention Center. Sat. 6 hrs. Contact: Verda Belyeu, Grossmont Hospital, Box 158, La Mesa 92044-0158. (619) 589-4153.

May 6-10—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. 32 hrs. $485. Contact: UCSD.

June 8-9—**Clinical Toxicology and Emergency Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $310. Contact: UCSF.

June 24-28—**Postgraduate Institute for Primary Care & Emergency Physicians Emergency Medicine Symposium III: Pediatrics, OB/GYN, Dermatology, Legal Aspects, Etc.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $260-$485. Contact: UCSD.

August 7-11—**Wilderness Medicine:'91.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Program Director, Box 321, Yreka 96097. (800) 888-5632.

August 19-23—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriot, La Jolla. Mon-Fri. 32 hrs. $485. Contact: UCSD.

August 23-26—**Advances in Emergency Medicine.** Kaiser Permanente at Grand Hyatt Wailea Resort and Spa, Maui, Hawaii. Fri-Mon. Contact: Pat Salber, MD, Kaiser Permanente Hospital, 2200 O'Farrell, San Francisco 94115-3395.

FAMILY PRACTICE/PRIMARY CARE

March 15-17—**Psychopharmacology for the Primary Care Physician.** UCSD at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 16—**Orthopedics and Sports Medicine in Primary Care.** Scripps Clinic and Research Foundation at Amphitheater of the Green Hospital, La Jolla. Sat. 6 hrs. $125. Contact: Laurie Jones, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

March 22-23—**Management of Occupational Health Problems in Primary Care Settings.** UC Berkeley at Le Baron Hotel, San Jose. Fri-Sat. $225. Contact: Marion Gillen, (415) 642-5507.

March 27-29—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Cathedral Hill Hotel, San Francisco. Wed-Fri. 16 hrs. Contact: UCSF.

April 6-13—**Primary Care Medicine: Update '91.** UCSF at Waiohai Kauai, Hawaii. 1 week. 20 hrs. $525. Contact: UCSF.

April 26-28—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village, San Diego. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 10-14—**UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

July 8-11—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

August 23-25—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

March 15-21—**Internal Medicine 1991: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 23—**Diabetes Care Program, "New Pathways for the '90s."** Grossmont Hospital at San Diego Princess Hotel. Sat. 6 hrs. $100. Contact: Terri Francis, (619) 589-4810.

April 20—**Growth Factors in Clinical Medicine.** Scripps Clinic and Research Foundation at La Jolla. Sat. 4 hrs. $75. Contact: Laurie Jones, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

May 13-17—**Advances in Internal Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $585. Contact: UCSF.

May 25-27—**1991 CSIM Annual Meeting: Controversies, Challenges, Changes, and Calamari.** CSIM at Monterey Plaza Hotel. Sat-Mon. Contact: Cynthia Eaton, CSIM, Box 880606, San Francisco 94188-0606. (415) 882-5198.

August 26-28—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

OB/GYN

April 10-14—**Pacific Coast Fertility Society Annual Scientific Program.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 5820 Wilshire Blvd, No 500, Los Angeles 90036. (213) 937-5514.

August 9-11—**4th Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: Memorial/UCI Center for Health Education, Box 1428, Long Beach 90801. (213) 595-3811.

August 16-18—**Office Gynecology for the Primary Care Physician.** San Diego State University at the Hyatt Islandia, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

March 13-17—**Mountain Medicine: '91.** American College of Emergency Physicians at Squaw Valley. Wed-Sun. 22 hrs. $395. Contact: Howard Donner, MD, PO Box 321, Yreka 96097. (800) 888-5632.

OPHTHALMOLOGY

March 23—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. $120. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

May 17-19—**California Association of Ophthalmology Annual Meeting.** CAO at Sheraton Grande Torrey Pines, La Jolla. Fri-Sun. Contact: Linda Xyz, (415) 777-3937.

(Continued on Page 274)

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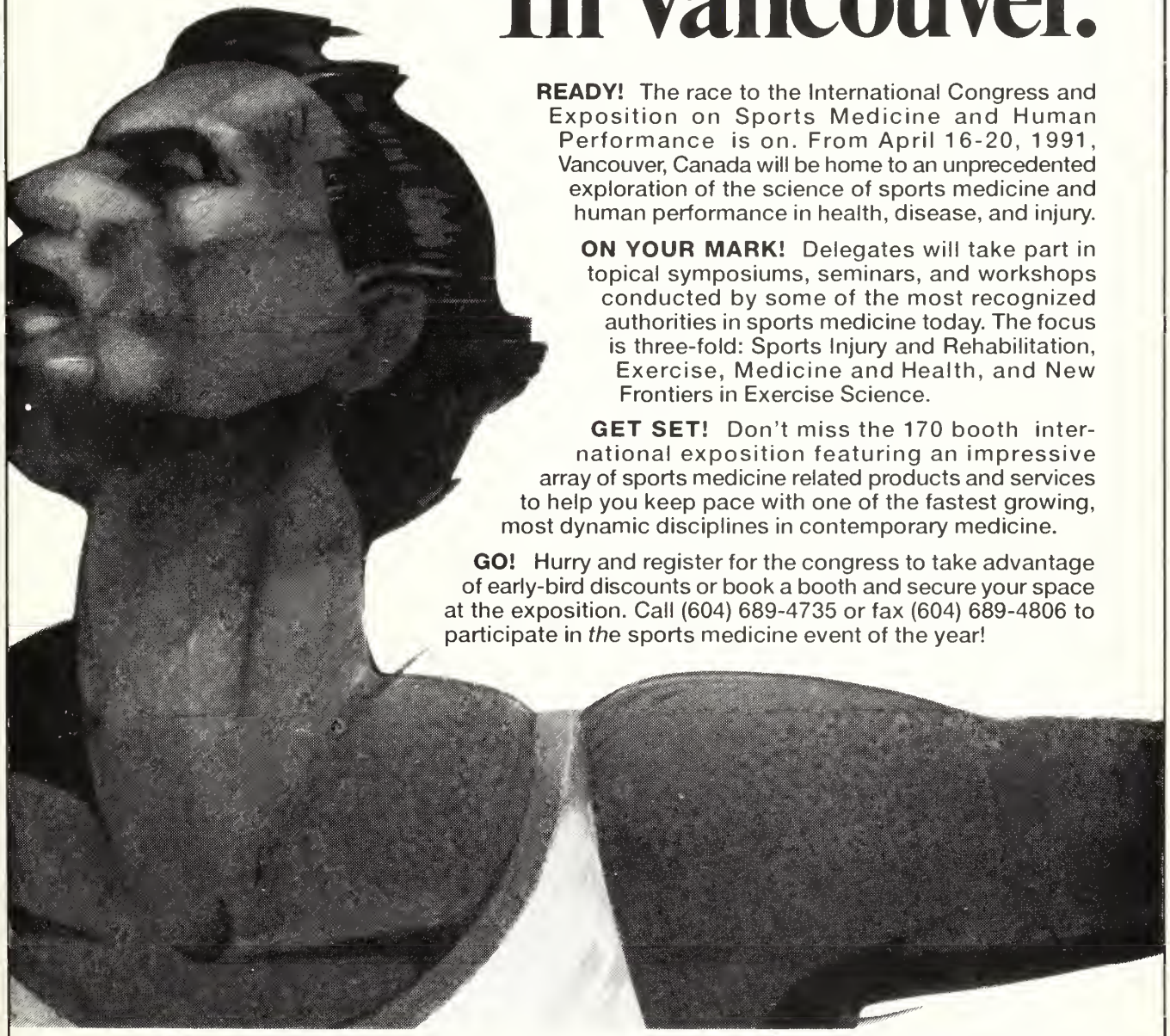

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CONTINUING MEDICAL EDUCATION

(Continued from Page 272)

PATHOLOGY

April 6—**6th Annual Conference: New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Amphitheater of Green Hospital, La Jolla. Sat. 7 hrs. $125. Contact: Laurie Jones, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

April 17-19—**12th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. $395. Contact: UCSF.

July 15-19—**Advances in Gastroenterology.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 19-22 hrs. $425. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 9-10—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684.

PEDIATRICS

April 5-6—**Annual Ambulatory Pediatrics.** UCD at Radisson Hotel, Sacramento. Fri-Sat. Contact: UCD.

April 8-10—**Injury Control for Children and Youth: The Fifth Annual California Conference.** North County Services at Red Lion Hotel, Costa Mesa. Mon-Wed. 17.5 hrs. Contact: Cynthia Cargill, North County Health Services, 348 Rancheros Dr, San Marcos 92069. (619) 471-2100.

April 11-13—**Nevada Neonatal-Pediatric Conference.** Humana Children's Hospital at Sands Hotel and Casino, Las Vegas. Thurs-Sat. 15 hrs. $200. Contact: Evelyn Bethel, (702) 733-4944.

April 13-14—**Pediatric Update 1991.** Children's Hospital Oakland at Jack London's Waterfront, Oakland. Sat-Sun. 11 hrs. $250. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

April 18-19—**10th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. Contact: UCD.

May 16-18—**24th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 1—**Special Children: Pediatric Perspectives in the '90s.** Children's Hospital at Merritt Peralta Health Education Center, Oakland. Sat. 7 hrs. $150. Contact: Kim Leadon, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

June 21-23—**Current Concepts in Child Neurology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 15 hrs. Contact: Children's Hospital, (619) 576-4072.

August 19-21—**Pediatrics Update: 1991.** San Diego State University at the Hyatt Islandia, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

April 27-28—**The Cutting Edge: Being a Better Therapist.** UCSD at La Jolla Marriott, San Diego. Sat-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

RADIOLOGY

March 15-17—**OB/GYN and Abdominal Sonography: Update 1991.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sun. 14.5 hrs. Contact: UCSF.

March 16-18—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. 16 hrs. $350. Contact: UCSF.

March 18-22—**34th Annual Diagnostic Radiology Postgraduate Course.** UCSF at the Fairmont Hotel and Tower, San Francisco. Mon-Fri. 33 hrs. Contact: UCSF.

April 7-12—**Diagnostic Imaging: 1991.** UCSF at Ritz-Carlton Mauna Lani, Kona, Hawaii. Sun-Fri. 23 hrs. $595. Contact: UCSF.

April 21-26—**11th Annual San Diego Resident's Radiology Review Course.** UCSD at Hyatt Regency Hotel, La Jolla. Sun-Fri. 39 hrs. $435. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 27—**Introduction to Interventional Radiology.** UCSD at Hyatt Regency Hotel, La Jolla. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 18-21—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, Coronado. Thurs-Sun. 19.5 hrs. $400. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

(Continued on Page 276)

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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SPECIAL ISSUES

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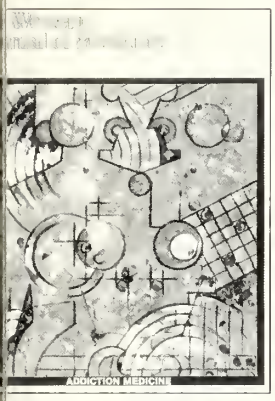

May 1990

Addiction Medicine
and the Primary Care Physician

- Overview of Addiction Medicine *David Smith, Editor/Founder, Haight-Ashbury Free Clinic*
- Chemical Dependence and the Work Place *John Osterloh and Charles Becker*
- The Disease Concept of Alcoholism *John Wallace*
- Cognitive Impairments in Recovering Alcoholics *George Fein*
- Substance Abuse and Pulmonary Pathology *Donald Tashkin*
- Special Populations: The Adolescent *Martha Morrison*
- Methadone Maintenance in the Treatment of Opioid Dependence *Joan Zweben*
- Treatment of Nicotine Dependence in the Chemically Dependent Patient *Karen Sees*
- Pharmacologic Approaches to the Treatment of Cocaine Dependence *Wanda A. Taylor and Mark S. Gold*

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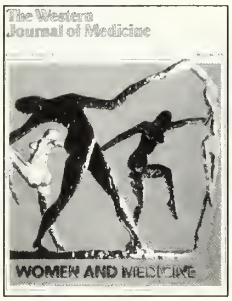
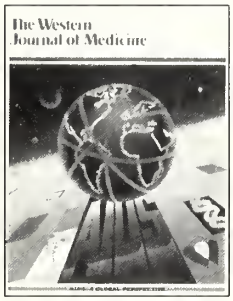
ross-cultural medi- cine is devoted to are of patients of rent, cultural, ethnic, ligious backgrounds. ects include South-Asian refugees in American health care em, psychiatry and ese culture, health illness in Filipino igrants, and health of Middle Eastern ents. M. Margaret k, PhD, Special Issue or, 1983. 3rd printing.

Women and Medicine



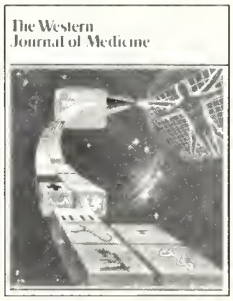
This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

AIDS— A Global Perspective



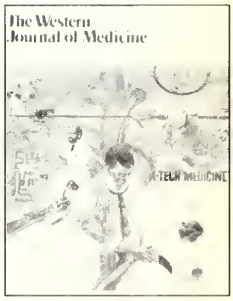
This issue, from the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent. Jonathan M. Mann, MD, Special Issue Editor, 1987.

Medical Informatics



Medical Informatics explores the capabilities and potential capabilities of new electronic methods of collecting, processing, storing, analyzing, and using information to advance medical science and improve patient care. Marsden S. Blois, MD, Special Issue Editor, 1986.

High-Tech Medicine



This issue examines high-tech medicine as it pertains to patient care. Subjects include lasers in ophthalmology, cutaneous laser therapy, magnetic resonance imaging, organ transplantation, positron emission tomography, and modern molecular biology. R. Paul Robertson, MD, Special Issue Editor, 1985.

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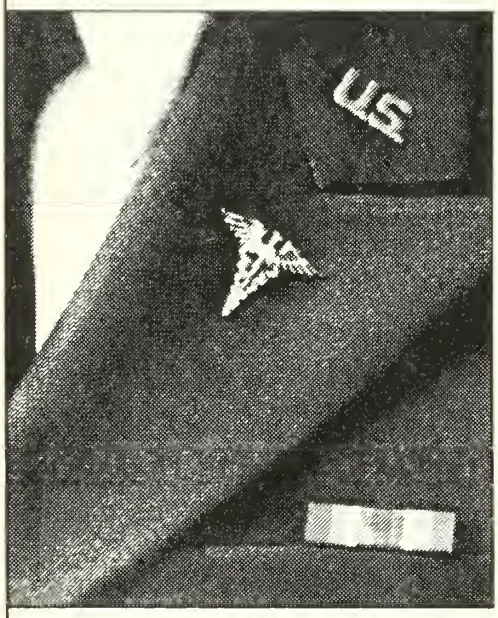

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CONTINUING MEDICAL EDUCATION

(Continued from Page 274)

July 22-24—**Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Wed. 14 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-27—**5th Annual MRI Symposium Including: Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Sat. 31 hrs. $695. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 25-28—**5th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 18 hrs. $375. Contact. Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

August 12-16—**Radiology for Clinicians.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 11-13—**The 7th Annual Sonography Update Conference and Exhibit.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 14-15—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 23-26—**Applied Ultrasound: Accent on Doppler.** University of Alabama at Birmingham at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 25-28—**Diagnosis of Musculoskeletal Disorders: State of the Art.** International Skeletal Society at Hotel del Coronado, San Diego. Wed-Sat. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

May 17-18—**What's New in Rehabilitation?** Memorial/UCI Center for Health Education at Queen Mary, Long Beach. Fri-Sat. Contact: UCI.

SURGERY

March 21-23—**Annual Aesthetic Surgery Symposium: Aesthetic Surgery of the Breast.** UCSF and Davies Medical Center. Thurs-Sat. Contact: UCSF.

April 29-May 1—**11th Annual Scientific Meeting and Exhibition.** American Society for Laser Medicine and Surgery at the Sheraton on Harbor Island, San Diego. Mon-Wed. Contact: ASLMS, 2404 Stewart Square, Wassau, WI 54401. (715) 845-9283

May 2-4—**Advances in Knee Reconstruction Surgery: Ligament Reconstruction, Unicompartmental Replacement, and Patellofemoral Joint.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 26-hrs. $600. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 15-19—**13th Annual Wound Management Workshop: May.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 19 hrs. Contact: UCSD.

MULTIPLE TOPICS

March 22-23—**Women's Nutrition and Health: Annual Clinical Nutrition Program.** UCD at Embassy Suites, Napa. Fri-Sat. 13 hrs. Contact: UCD.

April 19-20—**HIV Update.** UCD at Holiday Inn Holidome, Sacramento. Fri-Sat. 12 hrs. Contact: UCD.

April 25-28—**Nevada State Medical Association Annual Meeting.** NSMA at Quail Lodge, Carmel. Thurs-Sun. Contact: Nevada State Medical Association, 3660 Baker Ln, Reno, NV 89502. (702) 825-6788.

February 20-23—**The Practicing Physician's Approach to the Difficult Headache Patient.** Scripps Clinic and Diamond Headache Clinic at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, 5252 N Western Ave, Chicago, IL 60625. (312) 878-5558.

(Continued on Page 278)

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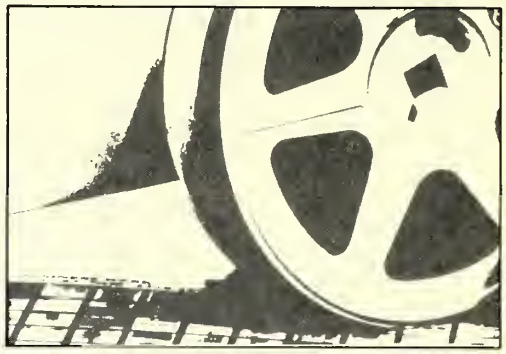

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CONTINUING MEDICAL EDUCATION

(Continued from Page 276)

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

March 16-23—**14th Annual Urology Conference.** Rose Medical Center at Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**13th Annual Sports Medicine Conference.** Rose Medical Center, Marriott's Mark Resort, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 16-23—**Computers in Medicine Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

March 19—**Mesothelioma.** Lutheran Medical Center Auditorium, Wheat Ridge. Tues. Noon Conference. Contact: Cary L. Walker, (303) 425-2009.

March 23-30—**14th Annual Cancer Treatment Conference.** Rose Medical Center at The Antlers at Vail, Vail. One week. Contact: David R. Scott, 1 (800) 525-5810.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO (303) 270-5195.

March 26—**Newer Treatments of Osteoporosis.** Lutheran Medical Center, Wheat Ridge. Tues. Noon Conference. Contact: Cary L. Walker, (303) 425-2009.

April 14-16—**Conference on Alcohol and Other Drug Issues.** Alcohol and Drug Abuse Division (ADAD), Colorado Department of Health at University Park Holiday Inn, Fort Collins. Sun-Tues. Contact: Sylvia J. Kornelsen, (303) 756-8380.

September 27-28—**Montrose Fall Clinics for Physicians.** Montrose Memorial Hospital, Montrose. Fri-Sat. Contact: Kathy Holman, (303) 240-7397.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

IDAHO

March 21-22—**Idaho Thoracic Society—Annual Medical Symposium.** Anderson Center, Boise. Thurs-Fri. Contact: Idaho Thoracic Society, PO Box 33, Boise 83707. (208) 344-6567.

April 25-28—**Comprehensive Review in Toxicology.** Idaho Poison Center, Boise. Thurs-Sun. 20 hrs. Contact: Dennis Emerson or Robin Clark, Idaho Poison Center, 1055 N Curtis Rd, Boise 83706. (208) 378-2159.

May 13-15—**Idaho Academy of Family Physicians—43rd Annual Meeting.** The Coeur d'Alene, Coeur D'Alene. Mon-Wed. Contact: Mrs Irma Sparks, Exec Dir, IAFP, PO Box 175, Boise 83701.

July 25-27—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

(Continued on Page 280)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 278)

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 16—**AIDS Update.** University of New Mexico School of Nursing and Pharmacy Auditorium, Albuquerque. Sat. Contact: Marsha VerPloegh, Psychiatric Medical Association, PO Box 26666, Albuquerque 87125. (505) 291-5375.

April 5-6—**Genetics for the Obstetrician.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: Mary R. Boning, Presbyterian Healthcare Services, PO Box 26666, Albuquerque 87125. (505) 841-1225.

April 5-6—**13th Annual Pediatric Cardiopulmonary Update.** Hyatt Regency, Albuquerque. Fri-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

May 9-10—**New Mexico Medical Society Annual Meeting.** Albuquerque. Thurs-Fri. Contact: Glenn Taylor, NMMS, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or 1 (800) 748-1596.

August 5-9—**Body Imaging: Ultrasound, CT, MR, Nuclear Medicine.** El Dorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

March 16—**Hans Hecht Memorial Lecture** (Sponsor: UUMC). Sat. University of Utah, Salt Lake City. Contact: (801) 581-8664.

March 22-24—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: J. Freedman, (801) 581-7001.

March 28—**Infofair** (Sponsor: UUMC). Thurs. Spencer S. Eccles Health Sciences Library, University of Utah, Salt Lake City. Contact: (801) 581-5762.

(Continued on Page 282)

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[1] FDA survey, "Patient Receipt of Rx Drug Information", 1983

[2] A Study of Attitudes, Concerns, and Information Needs for Rx Drugs and Related Illnesses, CBS Television Network Consumer Model Survey, 1983

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(Continued from Page 280)

April 4—**Respiratory Tract Infections** (Sponsor: UUMC). Thurs. Deer Valley. Contact: (801) 581-8664.

April 5-6—**Hypertension** (Sponsor: UUMC). Fri-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

April 13—**Sports Medicine Update** (Sponsor: UUMC). Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

May 3-4—**Surgical Infections** (Sponsor: UUMC). Fri-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

May 10—**Ophthalmology, Annual Resident's Day, Clinical Conference** (Sponsor: UUMC). Fri. University of Utah, Salt Lake City. Contact: (801) 581-8664.

May 10-11—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

May 17—**Infectious Disease Update** (Sponsor: UUMC). Fri. Skaggs Hall Auditorium, University of Utah, Salt Lake City. Contact: (801) 581-8664.

May 30-31—**Communications Disorders** (Sponsor: UUMC). Thurs-Fri. Snowbird. Contact: (801) 581-8664.

June 9-11—**Interactive Video in Health Education—'Slice of Life'** (Sponsor: UUMC). Sun-Tues. University of Utah, Salt Lake City. Contact: (801) 581-8664.

June 17-21—**University of Utah School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Mon-Fri. University of Utah, Salt Lake City. Contact: (801) 581-8664.

July 8-13—**Update in Internal Medicine: Focus on Ambulatory Care Medicine** (Sponsor: UUMC). Sat-Thurs. Snowbird. Contact: (801) 581-8664.

July 12-14—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

September 27-29—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UMA: Utah Medical Association, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

March 15—**Inflammatory Bowel Disease.** Seattle. Fri. Contact: VMMC.

March 22-23—**Ophthalmology (WSAO)—Annual President's Meeting.** Seattle. Fri-Sat. Contact: (206) 441-9762.

April 1-6—**General Practice Review.** Scottsdale, Arizona. Mon-Sat. Contact: Pacific Northwest Educational Institute, (206) 258-6322.

April 3-4—**Cumulative Trauma Disorders of Upper Extremities.** Seattle. Sun-Mon. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 4-5—**Aging and the Elderly.** Seattle. Mon-Tues. Contact: U/W.

April 11-12—**HIV/AIDS—Learning to Communicate Effectively to Reduce Patient Risk: An Experiential Workshop for Primary Care Providers.** Seattle. Thurs-Fri. Contact: U/W AIDS Education and Training Center, (206) 720-4250.

April 12-13—**Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS CME.

April 12-13—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 13-14—**Benton-Franklin County Medical Society Annual Meeting.** Tri-Cities. Sat-Sun. Contact: (509) 783-8616.

April 15-18—**The Best Approach 1991: Effective, Efficient Strategies in Cardiology, Orthopedics, Gastroenterology, and Pediatrics.** Kauai Sheraton, Hawaii. Fri-Mon. Contact: Group Health, (206) 326-3441.

April 15-26—**PM & R Review.** Seattle. Fri-Tues. Contact: U/W.

April 26-27—**Medical Issues of Active and Athletic Women.** Seattle. Fri-Sat. Contact: VMMC.

April 30-May 1—**AIDS Symposium: Pathogenesis of HIV Infection.** Spokane. Tues-Wed. Contact: WSU, (509) 335-2349.

May 1-3—**ACP: Clinical Topics in Pulmonary Medicine.** Seattle. Fri-Sat. Contact: VMMC.

May 9—**OB/GYN.** Everett. Thurs. Contact: (206) 258-6322.

May 10—**Office Procedures.** Tacoma. Fri. Contact: PCMS.

May 11—**Corneal Update.** Seattle. Sat. Contact: VMMC.

May 31—**Office Gynecology—1991.** Tacoma. Fri. Contact: PCMS.

June 1—**Substance Abuse.** Seattle. Sat. Contact: U/W.

June 7-8—**Topics in General Medicine.** Seattle. Fri-Sat. Contact: VMMC.

June 15—**Horizons in Urology.** Seattle. Sat. Contact: U/W.

June 24-25—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: VMMC, (206) 627-7137.

July 26-28—**Seafair XII: Regional Anesthesia.** Seattle. Fri-Sun. Contact: VMMC.

August 9-11—**International Conference on Pancreatic Cancer.** Seattle. Fri-Sun. Contact: VMMC.

September 12-13—**Resolving the Ethical Dilemmas in Animal Protocol Review.** Seattle. Thur-Fri. Contact: U/W.

September 26—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

December 6-7—**Urology.** Seattle. Fri-Sat. Contact: (206) 441-9762.

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 13-15—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
• Discontinue Ceclor in the event of allergic reactions to it.
• Prolonged use may result in overgrowth of nonsusceptible organisms.
• Positive direct Coombs' tests have been reported during treatment with cephalosporins.
• Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
• Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
• Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
• Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of **serum-sickness-like** reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
• Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
• Gastrointestinal (mostly diarrhea): 2.5%
• Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
• As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
• Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
• Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

Abnormalities in laboratory results of uncertain etiology.
• Slight elevations in hepatic enzymes.
• Transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia.
• Rare reports of increased prothrombin time with or without clinical bleeding in patients receiving Ceclor and Coumadin concomitantly.
• Abnormal urinalysis; elevations in BUN or serum creatinine.
• Positive direct Coombs' test.
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2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)
4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983
7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

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Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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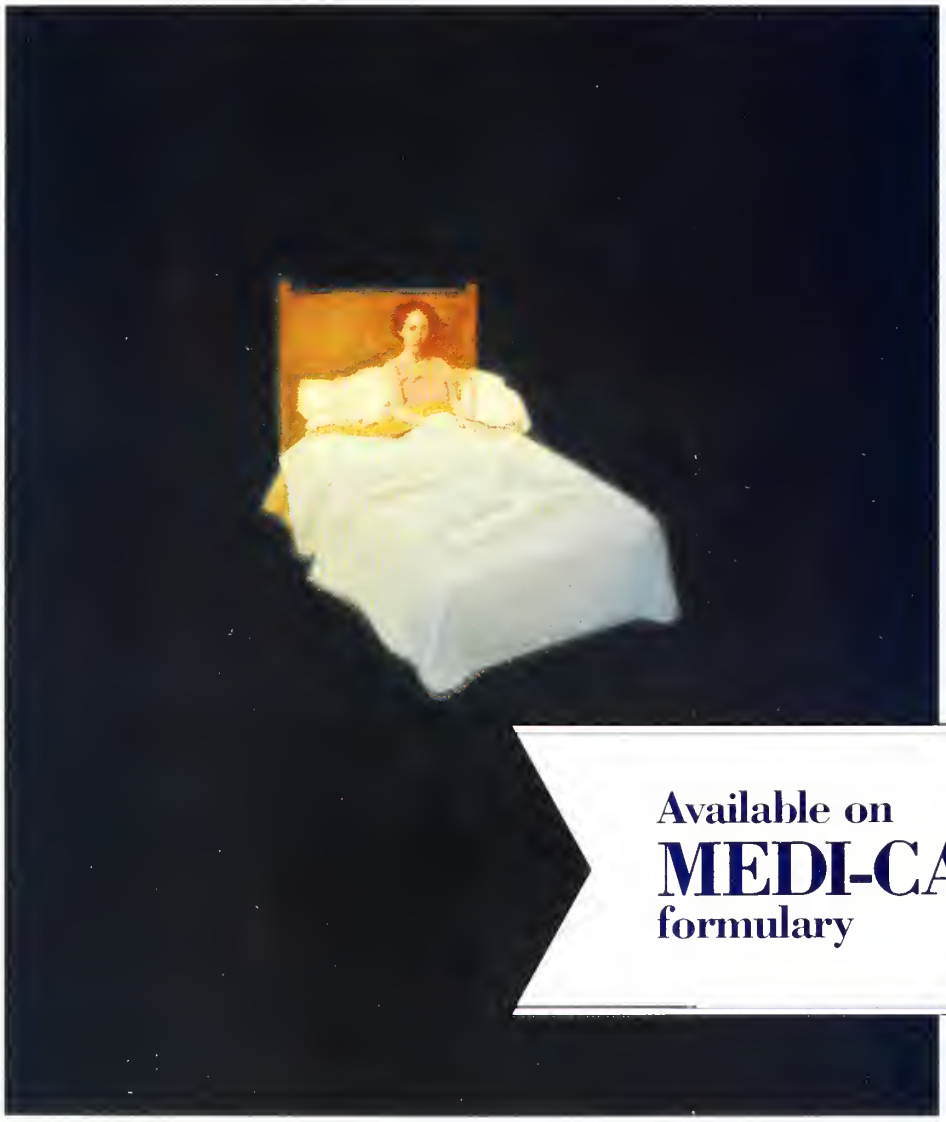

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Daytime performance with ProSom was shown to be comparable to placebo-treated patients, with performance deficits, if any, shown to be short and transient.[6] And clinical studies, including a 10-week efficacy trial, demonstrated no anterograde amnesia or short-term memory impairment.[6,7]

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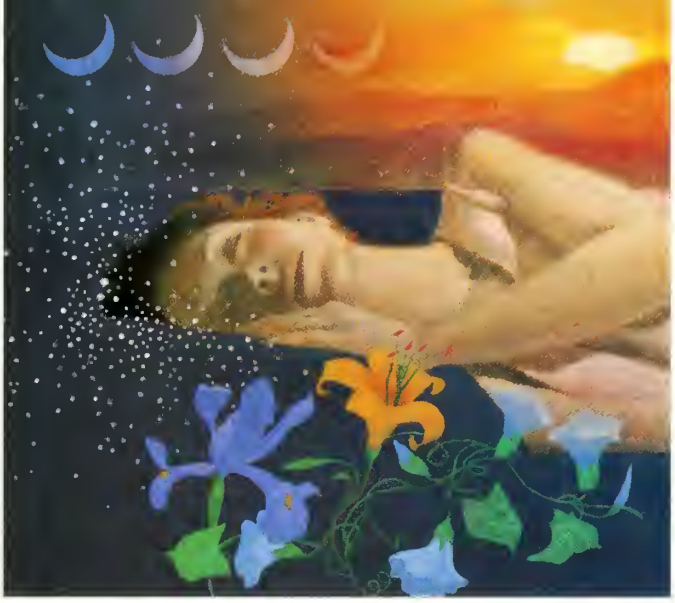

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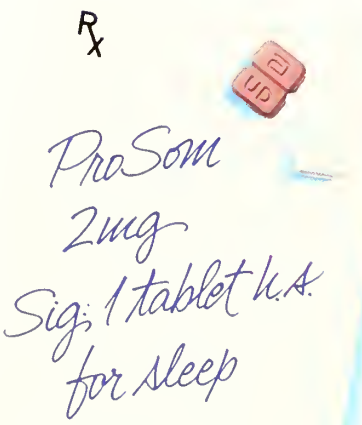

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1 Lamphere J, Roehrs T, Zorick F, Koshorek G, Roth T. Chronic hypnotic efficacy of estazolam. *Drugs Exp Clin Res* 1986;12(8):687-691.
2 Pierce MW, Shu VS. Efficacy of estazolam: The United States clinical experience. *Am J Med* 1990;88(3A):6S-11S.
3 Walsh JK, Targum SD, Pegram V, et al. A multi-center clinical investigation of estazolam: short-term efficacy. *Curr Ther Res* 1984;36(5):866-874.
4 Dominguez RA, Goldstein BJ, Jacobson AF, Steinbook RM. Comparative efficacy of estazolam, flurazepam, and placebo in outpatients with insomnia. *J Clin Psychiatry* 1986;47(7):362-365.
5 Roehrs T, Zorick F, Lord N, Koshorek GL, Roth T. Dose-related effects of estazolam on sleep of patients with insomnia. *J Clin Psychopharmacol* 1983;3(3):152-156.
6 Pierce MW, Shu VS, Groves LJ. Safety of estazolam: The United States clinical experience. *Am J Med* 1990;88(3A):12S-17S.
7 Scharf MB, Mayleben DW, Fletcher KA, Shu VS, Pierce MW. Effect of single doses of estazolam and triazolam on memory function in adult insomniacs. Submitted for publication.

Brief Summary

CLINICAL PHARMACOLOGY:
The range of estimates for the elimination half-life varied from 10 to 24 hours. Benzodiazepine clearance is accelerated in smokers compared to nonsmokers, and there is evidence that this occurs with estazolam. This decrease in half-life, presumably due to enzyme induction by smoking, is consistent with other drugs with similar hepatic clearance characteristics. In all subjects the mean elimination half-life appears to be independent of the dose.

CONTRAINDICATIONS:
Contraindicated in pregnant women due to potential fetal damage. Women of childbearing age should be warned of the potential risk to the fetus.

WARNINGS:
Due to CNS-depressant effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and about possible combined effects with alcohol and other CNS-depressant drugs.

As with all benzodiazepines, amnesia, paradoxical reactions, and other adverse behavioral effects may occur.

There have been reports of withdrawal symptoms of the type associated with CNS depressants following rapid decrease or abrupt discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

PRECAUTIONS:
General: Impaired motor and/or cognitive performance attributable to accumulation of benzodiazepines and active metabolites is a concern in certain patients (eg, those sensitive to benzodiazepines or those with a reduced capacity to metabolize and eliminate them) (see DOSAGE AND ADMINISTRATION). Elderly or debilitated patients and those with impaired renal or hepatic function should be advised to monitor themselves for signs of excessive sedation or impaired conditions.

May cause dose-related respiratory depression that is ordinarily not clinically relevant at recommended doses in patients with normal respiratory function. Monitor patients with compromised respiratory function appropriately.

Administered with caution to patients exhibiting symptoms of depression. Suicidal tendencies and intentional overdosage is more common in such patients.

Information for Patients: Inform patients about consumption of alcohol and other drugs; possible fetal damage and excretion in breast milk; hazards of operating machinery or driving; not increasing dose; and worsening of sleep after abrupt discontinuation.

Laboratory Tests: Not ordinarily required in healthy patients. When treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable.

Drug Interactions: Benzodiazepines may be potentiated by anticonvulsants, antihistamines, alcohol, barbiturates, monoamine oxidase inhibitors, narcotics, phenothiazines, psychotropic medications, or other drugs that produce CNS depression. Smokers have increased clearance of benzodiazepines (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were conducted in mice and rats at doses of 0.8, 3, and 10 mg/kg/day and 0.5, 2, and 10 mg/kg/day, respectively. Evidence of tumorigenicity was not observed. Hyperplastic liver nodules were increased in female mice given mid- and high doses. The significance of such nodules in mice is not known. *In vitro* and *in vivo* mutagenicity tests did not show a mutagenic potential. Fertility in male and female rats was not affected by doses up to 30 times the usual recommended human dose.

Pregnancy: May cause fetal damage if administered during pregnancy. The child born of a mother taking benzodiazepines may be at risk for withdrawal symptoms and neonatal flaccidity during the postnatal period.

Labor and Delivery: No established use.

Nursing Mothers: Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness below the age of 18 not established.

Geriatric Use: Approximately 18% of patients studied were 60 years or older. The adverse event profile did not differ from that observed in younger individuals. Exercise care when prescribing to small or debilitated elderly patients (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS:
During clinical trials in which ProSom was administered to 1277 patients, the most commonly observed adverse events were somnolence, hypokinesia, dizziness, and abnormal coordination. The events listed below were also observed. Although these events occurred during treatment with ProSom, they were not necessarily caused by it.

Body as a Whole: abdominal pain, allergic reaction, asthenia, back pain, body pain, chest pain, chills, edema, fever, headache, jaw pain, lower extremity pain, malaise, neck pain, swollen breast, upper extremity pain. *Cardiovascular System:* arrhythmia, flushing, palpitation, syncope. *Digestive System:* constipation, decreased appetite, dry mouth, dyspepsia, enterocolitis, flatulence, gastritis, increased appetite, melena, mouth ulceration, nausea, vomiting. *Endocrine System:* thyroid nodule. *Hematologic and Lymphatic System:* leukopenia, purpura, swollen lymph nodes. *Metabolic/Nutritional Disorders:* increased SGDT, thirst, weight gain, weight loss. *Musculoskeletal System:* arthralgia, arthritis, muscle spasm, myalgia, stiffness. *Nervous System:* agitation, amnesia, anxiety, apathy, ataxia, circumoral paresthesia, confusion, coordination abnormal, decreased libido, decreased reflexes, depression, dizziness, dream abnormal, emotional lability, euphoria, hallucinations, hangover, hostility, hypokinesia, nervousness, neuritis, nystagmus, paresthesia, seizure, sleep disorder, somnolence, stupor, thinking abnormal, tremor, twitch. Minor changes in EEG patterns, usually low-voltage fast activity, were observed during therapy or withdrawal and are of no known clinical significance. *Respiratory System:* asthma, cold symptoms, cough, dyspnea, epistaxis, hyperventilation, laryngitis, pharyngitis, rhinitis, sinusitis. *Skin and Appendages:* acne, dry skin, pruritis, rash, sweating, urticaria. *Special Senses:* abnormal vision, decreased hearing, diplopia, ear pain, eye irritation, eye pain, eye swelling, perverse taste, photophobia, scotomata, tinnitus. *Urogenital System:* frequent urination, hematuria, menstrual cramps, nocturia, oliguria, penile discharge, urinary hesitancy, urinary incontinence, urinary urgency, vaginal discharge/itching. *Postintroduction Reports:* Voluntary reports from non-US postmarketing experience have included rare occurrences of photosensitivity and agranulocytosis. Due to the uncontrolled nature of these reports, a casual relationship has not been determined.

DRUG ABUSE AND DEPENDENCE:
Controlled Substance: Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuation of benzodiazepines. Symptoms range from mild dysphoria and insomnia to abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. Patients with a history of seizures are at increased risk. Withdraw gradually in patients taking benzodiazepines for a prolonged period. Monitor addiction-prone patients closely.

DOSAGE AND ADMINISTRATION:
Initial dose for adult and healthy elderly patients is 1-2 mg at bedtime. Increase dose carefully in the elderly. Consider an initial dose of 0.5 mg in small or debilitated older patients.

HOW SUPPLIED:
Available in 1 mg and 2 mg scored tablets.

Store below 86°F (30°C).

Revised January, 1991

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Biomedical Science

Acetazolamide or Dexamethasone Use Versus Placebo to Prevent Acute Mountain Sickness on Mount Rainier

ALLAN J. ELLSWORTH, PharmD; ERIC F. MEYER, MD; *and* ERIC B. LARSON, MD, MPH, *Seattle, Washington*

Eighteen climbers actively ascended Mount Rainier (elevation 4,392 m) twice during a randomized, double-blind, concurrent, placebo-controlled, crossover trial comparing the use of acetazolamide, 250 mg, dexamethasone, 4 mg, and placebo every 8 hours as prophylaxis for acute mountain sickness. Each subject was randomly assigned to receive placebo during one ascent and one of the active medications during the other ascent. Assessment of acute mountain sickness was performed using the Environmental Symptoms Questionnaire and a clinical interview. At the summit or high point attained above base camp, the use of dexamethasone significantly reduced the incidence of acute mountain sickness and the severity of symptoms. Cerebral and respiratory symptom severity scores for subjects receiving dexamethasone (0.26 ± 0.16 and 0.20 ± 0.19, respectively) were significantly lower than similar scores for both acetazolamide (0.80 ± 0.80 and 1.20 ± 1.05; $P = .025$) and placebo (1.11 ± 1.02 and 1.45 ± 1.27; $P = .025$). Neither the use of dexamethasone nor that of acetazolamide measurably affected other physical or mental aspects. Compared with placebo, dexamethasone appears to be effective for prophylaxis of symptoms associated with acute mountain sickness accompanying rapid ascent. The precise role of dexamethasone for the prophylaxis of acute mountain sickness is not known, but it can be considered for persons without contraindications who are intolerant of acetazolamide, for whom acetazolamide is ineffective, or who must make forced, rapid ascent to high altitude for a short period of time with a guaranteed retreat route.

(Ellsworth AJ, Meyer EF, Larson EB: Acetazolamide or dexamethasone use versus placebo to prevent acute mountain sickness on Mount Rainier. West J Med 1991 Mar; 154:289-293)

Acute mountain sickness (AMS) is a syndrome characterized by headache, nausea, vomiting, insomnia, and lassitude.[1] The syndrome, part of a continuum including high-altitude pulmonary edema[2] and high-altitude cerebral edema,[3] generally occurs in lowlanders three to eight hours after they ascend to an altitude greater than 3,000 m.[4,5] The increased popularity of recreation in mountain settings, along with the greater accessibility brought about by advances in transportation systems, has contributed to the increase in the incidence of AMS. Slow, staged ascent remains the best method of preventing AMS.[6] Interest continues in developing a prophylactic regimen that is rapid acting, effective, and well tolerated.

In the past, much of the interest concerning the chemoprophylaxis of AMS has focused on acetazolamide.[4,7-17] Recent studies, however, have shown the use of dexamethasone to be effective in reducing the incidence and severity of AMS symptoms.[18-22] A previous study comparing these two agents in different cohorts ascending Mount Rainier, an ideal setting for the study of AMS and prophylactic drug regimens under actual climbing conditions,[13,23] showed an acetazolamide-induced side effect (nausea) at low elevations, which confounded comparison of acetazolamide and dexamethasone.[20] In the present study, we have reexamined the efficacy of prophylactic acetazolamide and dexamethasone use relative to placebo during repeated, rapid, active ascents of Mount Rainier using a crossover design.

Patients and Methods

Eighteen climbers made two separate ascents of Mount Rainier scheduled at least two weeks apart. Using a random numbers table, climbers were allocated to receive one of two active chemoprophylactic drugs, dexamethasone and acetazolamide, to be taken during one of their ascents. During the other ascent, they received placebo. The order of active drug or placebo administration was assigned randomly as well. Dosage regimens consisted of either acetazolamide, 250 mg (Geneva Generics, lot 31578); dexamethasone, 4 mg (Roxane, lot 861121); or lactose placebo (MCB Reagents, lot LX0035-3) administered every 8 hours beginning 24 hours before the start of each climb and continuing until descent from the high point. The drugs were packaged in identical-appearing pink capsules by Pharmaceutical Services, University of Washington,* and distributed at orientation and baseline data-gathering sessions several days before each ascent.

The subjects normally resided at sea level and had not been exposed to high altitude within three weeks before the study. All were free of cardiorespiratory disease, and none had a history of diabetes mellitus, sulfa drug allergy, acid peptic disease, or psychiatric illness. The study was approved by the University of Washington Human Subjects Review Committee, and all subjects gave informed consent.

*Theodore Taniguichi, MS, Director of Pharmaceutical Services, Department of Pharmacy, University Hospital, University of Washington, prepared the medication.

From the Departments of Pharmacy Practice (Dr Ellsworth), Family Medicine (Drs Ellsworth and Meyer), and Medicine (Dr Larson), University of Washington, Schools of Pharmacy and Medicine, Seattle.

This work was presented in part at the Western Sectional Meetings, American Federation for Clinical Research, 1988 (abstract: Clin Res 1988; 36:172A). It was supported in part from United States Public Health Service grant No. 5 D15 PE80000 and the Medical Student Research Training Program, University of Washington School of Medicine.

The Camp Schurman Climbing Rangers, Mount Rainier National Park, assisted with this study.

Reprint requests to Allan Ellsworth, PharmD, Department of Family Medicine, RF-30, University of Washington, Seattle, WA 98195.

ABBREVIATIONS USED IN TEXT

AMS = acute mountain sickness
AMS-C = cerebral symptoms of acute mountain sickness
AMS-R = respiratory symptoms of acute mountain sickness
ANOVA = analysis of variance
CLAT = Conceptual Level Analogy Test
ESQ-III = Environmental Symptoms Questionnaire

Subjects drove from sea level to a trailhead at 1,300 m on the northeast side of Mount Rainier. Active ascent to a base camp at approximately 3,000 m took an average of seven hours. The ascent to the summit began early in the morning on the second day, required about seven hours, and was followed by the return to the trailhead the same day. Symptoms of AMS were assessed using the Environmental Symptoms Questionnaire, second revision (ESQ-III), a 67-question symptom inventory designed to quantitate the severity of symptoms (using a 6-point Likert scale) specifically associated with exposure to altitude and other stressful environments.[24] The questionnaire was self-administered by subjects at sea level (24 hours after they began taking the study medications) and during the climb, within 15 minutes of reaching the following points: 1,300 m (trailhead), 3,000 m (base camp) on ascent, 4,392 m (summit) or high point attained above base camp, and 3,000 m (base camp) on descent. Weighted averages of cerebral (AMS-C) and respiratory (AMS-R) symptom scores were calculated. Symptoms such as headache, nausea, and insomnia contributed to the AMS-C score while symptoms such as shortness of breath and rapid heartbeat contributed to the AMS-R score. As suggested by the results of earlier studies, scores of greater than 0.7 for AMS-C and 0.6 for AMS-R were used to indicate the presence of AMS.[24]

Immediately following completion of the questionnaire, a clinical interview and examination were conducted by one of the investigators (A.J.E.) without knowledge of the subjects' responses to the questionnaire. Scoring was based on a scale that assigns 1 point each for headache, insomnia, anorexia, and dizziness; 2 points each for vomiting and headache unrelieved by analgesics; and 3 points for dyspnea at rest, ataxia, and severe lassitude. Scores of 2 or greater are considered diagnostic of AMS.[25,26]

Additional measures of physical and mental function at sea level and at the summit or high point attained included a five-minute Harvard Step Test,[27] the Conceptual Level Analogy Test,[28] and a test of rapid alternating finger movement as an adaptation of the finger oscillation test.[29] Measurements of blood oxygen saturation and heart rate were attempted with a portable pulse oximeter but were unsuccessful because of cold temperatures.*

A split-plot analysis of variance (ANOVA)[30] was used to compare the efficacy of acetazolamide and dexamethasone use against that of placebo and each other. Drug type (placebo vs active chemoprophylaxis or dexamethasone vs acetazolamide) was a fixed categorical covariant. Altitude was a fixed linear covariant. The indices of AMS (AMS-C, AMS-R, and clinical interviews) were used as dependent variables. To check for differences in the two groups of climbers during the placebo climb (a check on the randomization scheme), Mann-Whitney rank sum statistics were computed.[31] Finally, Fisher's exact test[32] was used to evaluate the significance of contingency table analyses.†

*Bill Anton, RRT, Respiratory Therapy, University Hospital, assisted, and Ken Craig, Physio Control, Redmond, Washington, provided the pulse oximeters.

Results

Group comparisons of the 18 subjects based on active drug received (11 men and 7 women, mean age 34.6±9.2 years) are shown in Table 1. All but 2 of the 18 subjects (89%) reached the summit on at least one of their two climbs. These two subjects, both in the acetazolamide group, had AMS symptoms that prevented ascent when using both drug and placebo. Adverse weather conditions were responsible for the other failed summit attempts. The lowest high point attained by subjects completing the study was 3,871 m, and the

†Jim Hughes, MS, provided statistical consultation.

TABLE 1.—*Group Comparisons Based on Active Drug Prophylaxis**

Clinical Characteristic	*Acetazolomide, n = 8*	*Dexamethasone, n = 10*
Age, yr	32.6±3.9	36.2±2.4
Male, No. (%)	6 (75)	5 (50)
Previous Mt Rainier ascent, No. (%)	3 (38)	3 (30)
Past history of AMS, No. (%)	5 (62)	3 (30)
Time, base camp to high point, h	5.7±0.6	6.6±0.3
Total time to high point, h	24.8±0.0	25.6±0.5
Study drug taken, doses	7.0±0.5	7.1±0.3

AMS = acute mountain sickness

*Mean and standard error of the mean, except as noted.

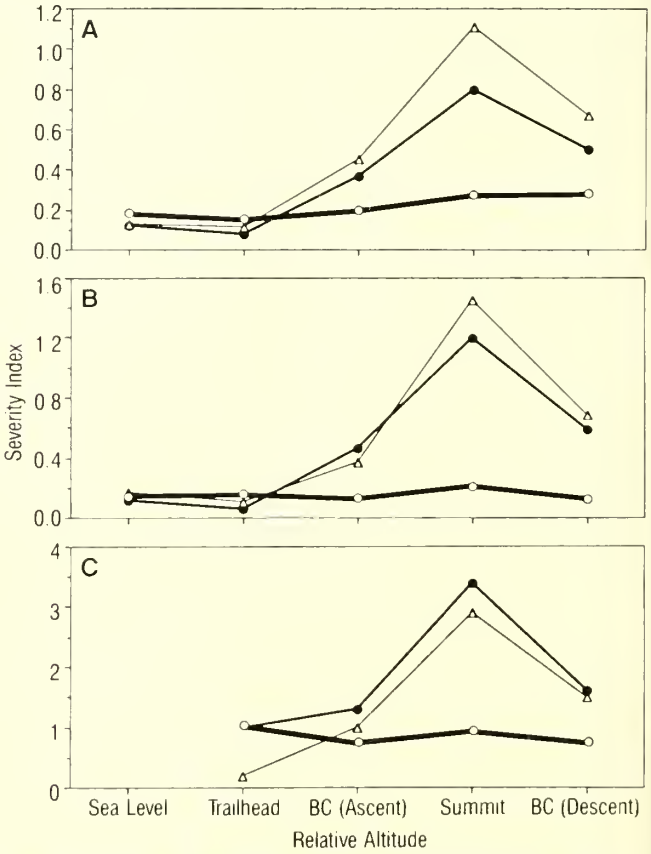

Figure 1.—The graphs show the relative severity of mean **(A)** cerebral symptoms index (AMS-C), **(B)** respiratory symptoms index (AMS-R), and **(C)** total interview scores for subjects receiving active and placebo prophylaxis against acute mountain sickness during a climb of Mount Rainier. BC = base camp, ● = acetazolamide, ○ = dexamethasone, △ = placebo

average time spent ascending from sea level to the high point was 25.2 hours (range, 21.0 to 27.5 hours). Of climbers assigned to receive dexamethasone, 30% had a previous history of AMS, compared with 62% of those receiving acetazolamide ($P = .18$).

At the summit or high point attained, the dexamethasone group had significantly fewer symptoms and a lower incidence of AMS than either the acetazolamide or placebo group as evaluated by both questionnaire and clinical interview (Figure 1). Cerebral symptom scores ($\pm$ standard deviation) at the high point for climbers receiving dexamethasone (0.26 ± 0.16) were significantly lower than those for climbers receiving acetazolamide (0.80 ± 0.80) and placebo (1.11 ± 1.02, $P = .025$). Similarly, AMS-R scores were lower for subjects receiving dexamethasone (0.20 ± 0.19) than for those using acetazolamide (1.20 ± 1.05) and placebo (1.45 ± 1.27, $P < .025$). The difference between the acetazolamide and placebo groups at the highest elevation was not statistically significant.

At the summit or high point (Figure 2), none of the subjects taking dexamethasone were designated "sick" by ESQ-III criteria[23] and only 10% were by clinical interview criteria.[24,25] By contrast, 40% of those taking acetazolamide were "sick" according to the ESQ-III ($P = .02$) and 75% were according to clinical interview ($P = .01$).

Overall, performance on the five-minute Harvard Step Test deteriorated in all groups (decrease from base line to high point: acetazolamide, 31%; dexamethasone, 20%; placebo, 35%) but was not significantly different by group. Similarly, there was little difference in mental function between groups. Conceptual Level Analogy Test (CLAT) scores were higher compared with placebo at the summit for climbers taking dexamethasone (mean score 13.1 ± 2.2 vs placebo 12.3 ± 2.9) and those taking acetazolamide (mean score 14.4 ± 3.1 vs placebo, 13.3 ± 2.8), not a significant difference. Comparison of the decline in CLAT scores by group also revealed no differences during the active drug climb (decline with dexamethasone use 21% vs placebo, 22%; decline with acetazolamide use 14% vs placebo, 20%). Dominant finger oscillation testing at the summit was not significantly different with the use of dexamethasone (55.0 ± 3.6) compared with placebo (49.7 ± 10.7) or receiving acetazolamide (52.0 ± 4.5) compared with placebo (54.0 ± 3.4).

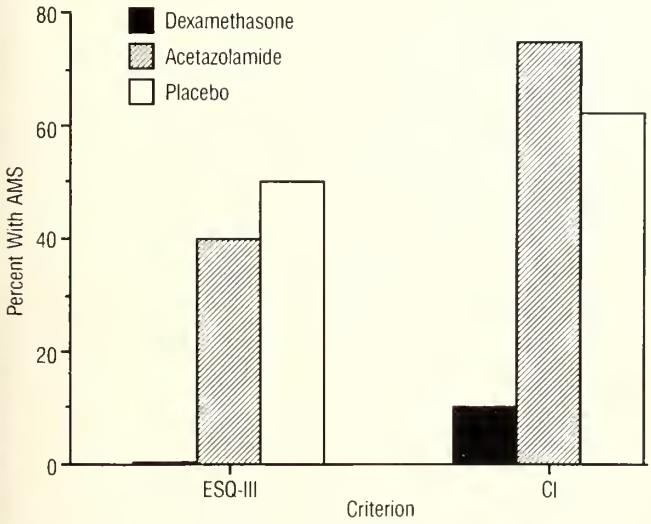

Figure 2.—A significant difference was found in the incidence of acute mountain sickness (AMS) at the summit or high point on Mount Rainier in subjects receiving prophylaxis with dexamethasone, acetazolamide, or placebo. The histograms on the left are based on Environmental Symptoms Questionnaire (ESQ-III) scores; those on the right are based on Clinical Interview (CI) scores. The group receiving dexamethasone reported a significantly lower percentage of AMS symptoms than those receiving either the acetazolamide or placebo ($P \leq .05$).

Eight of ten dexamethasone subjects, when asked which drug they preferred and while still blinded as to drugs used, preferred the drug climb to the placebo climb, whereas only three of eight acetazolamide subjects chose the drug climb.

Although subjects were randomly assigned to active drug groups and no statistically significant differences existed at base line in the study sample (Table 1), we were concerned about the possibility of confounding because a previous history of AMS appeared to be more frequent in the acetazolamide group. The climbers who reported a previous history of AMS did have higher symptom scores at the high point (AMS-C: AMS history, 1.2 ± 1.1, and no AMS history, 0.5 ± 0.5; AMS-R: AMS history, 1.6 ± 1.2, and no AMS history, 0.7 ± 0.9; clinical interview: AMS history, 2.5 ± 2.5, and no AMS history: 1.5 ± 1.5). Table 2 displays the paired differences between symptom scores on the placebo climb and the drug climb (for example, the AMS-C score while receiving dexamethasone minus the AMS-C score while taking placebo yields a mean paired difference for the AMS-C score without a previous history of AMS of -0.5 and for those subjects with a previous history of AMS of -1.2; negative paired differences indicate more favorable results). From these analyses, dexamethasone appears to be effective in reducing symptoms of AMS among all climbers, regardless of previous AMS history status. A greater degree of improvement is observed, however, among dexamethasone climbers with an AMS history. Acetazolamide use produced less dramatic and somewhat inconsistent improvements. These subgroup analysis results confirm our basic findings—dexamethasone use is effective in preventing symptoms of AMS. The small sample size of these subgroups made these estimates of symptom scores uncertain and limited our ability to ascertain statistical significance between the use of dexamethasone and that of acetazolamide because of the possible bias introduced by the slightly higher proportion of persons with a history of AMS among the climbers receiving acetazolamide.

Comments

In this study, the use of dexamethasone was effective in reducing the incidence and severity of AMS during the rapid, active ascent of Mount Rainier. The results validate our previous research, which used a different design and was complicated by the occurrence of gastrointestinal symptoms (nausea) at low elevations in the acetazolamide group.[20] The superiority of dexamethasone use reported here was not due to an adverse reaction to acetazolamide because acetazolamide-treated climbers had similar ESQ-III scores at the trailhead on both climbs. Overall, AMS-C, AMS-R, and clinical interview scores were increasingly more favorable for climbers taking dexamethasone, starting at base camp on ascent (3,000 m) and continuing to the summit or high point attained. The overall rate of AMS was significantly lower in the dexamethasone-treated subjects.

The relatively long history of safe and effective prophylactic acetazolamide is supported consistently by several

studies.[4,7-17] It is difficult to explain why acetazolamide was not as effective in this study, which is similar to previous work on Mount Rainier.[13] The lack of significant differences in the acetazolamide-treated group may be due to the small sample size. In addition, a previous history of AMS was more common (but not significantly so) in the group treated with acetazolamide. Nevertheless, subjects with and without a history of AMS generally had decreased symptoms with active acetazolamide treatment (Table 2). Side effects of acetazolamide use (including paresthesia, myopia, nausea and vomiting, dysgeusia, and urinary frequency) complicate blinding and cause problems of confounding because some side effects overlap with the symptoms of AMS. If dexamethasone use is relatively more effective than taking acetazolamide, this confounding may obscure the efficacy of acetazolamide use in direct comparison where the basis for comparison is primarily self-reported symptoms.

The mechanism by which dexamethasone, a potent synthetic corticosteroid, prevents symptoms of AMS is not known. Possible mechanisms include a reduction in cerebral blood flow or cerebral vasoconstriction and improved microcirculatory integrity, which may reduce edema by decreasing filtration through the microcirculation.[18,33-35] Levine and colleagues could show no objective differences between dexamethasone- and placebo-treated groups in oximetry data, other cardiac and respiratory measurements, or indirect measures of cerebral edema in chamber-induced AMS in six subjects.[36] They did show, as we and others have, that dexamethasone use reduced the severity of symptoms (by 63%). Although we attempted to investigate how dexamethasone use might prevent AMS by searching for objective correlates with dexamethasone treatment, these attempts were unsuccessful, and thus this study does not further elucidate the mechanism of action of dexamethasone. In fact, to our knowledge the only reported objective difference associated with the prophylactic effectiveness of dexamethasone is a reduction of retinal artery dilation in a hypobaric chamber.[18] Precise, portable methods and measurements are difficult to perform in field studies during actual climbing like ours. We attempted to collect blood oxygen saturation and heart rate data with a portable pulse oximeter, but this was not feasible because of cold temperatures. Further work is needed to elucidate the mechanisms of dexamethasone because subjective, self-reported scales may well be affected by dexamethasone's well-known euphoriant effects. The absence of this euphoriant effect at low elevations, however, detracts from this hypothesis as the primary mechanism of action.[37]

TABLE 2.—*Paired Symptom Score Differences (Drug Climb Score Minus Placebo Climb Score)**

	AMS-C		AMS-R		Clinical Interview	
Previous AMS History	*DEX*	*ACZ*	*DEX*	*ACZ*	*DEX*	*ACZ*
No						
Mean	−0.5†	0.4	−0.9†	−0.1	−1.3	−0.3
SD	0.8	0.8	1.3	1.5	2.4	2.1
n	7	2	7	3	7	3
Yes						
Mean	−1.2	−0.8	−1.8†	−0.6†	−3.0†	0.8
SD	1.5	1.3	1.7	0.6	3.0	2.5
n	3	5	3	5	3	4

ACZ = acetazolamide; AMS = acute mountain sickness; AMS-C = cerebral symptoms score; AMS-R = respiratory symptoms score, DEX = dexamethasone

*Negative paired differences indicate favorable results.
†$P < .05$ compared with placebo.

The use of dexamethasone for AMS prophylaxis is not without risks, and minimal field experience to date limits knowledge of the risk. Especially worrisome are severe side effects such as acute psychosis, depression,[22] glucose intolerance,[36] and drug withdrawal,[21] the risk of which must be weighed against the benign nature of AMS in most cases. Drug withdrawal at extreme altitude could lead to fatal complications and is a distinct possibility in extreme environments, where weather and injury frequently prevent climbers from descending on schedule and may strand climbing parties for long periods. In addition, the sustained use of glucocorticoids has been shown to accentuate anoxic brain damage in animals.[38]

More work is needed before the proper role of dexamethasone in AMS prophylaxis can be defined. For now, we agree with the conclusions of previous authors[39-41] that dexamethasone use for AMS prophylaxis should be considered only for those persons without contraindications who are intolerant of acetazolamide, for whom acetazolamide is ineffective, or who undergo forced, rapid ascent to high altitude for a short period with a guaranteed retreat route.

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THE FAIRYTALE TURNS BACKWARD

I'm afraid of this lake we walk around
where even mallards on the sunny log
bring one more question, and the long dives
of gulls call to you where you stand
on the stone bridge. Some spiteful fairy's
charming you toward darker water.
Enchanted by minnows and turtles,
by creatures of puddle and pond,
you're being pulled into green algae.

No matter how many kisses I give you
you go away from me, changing into cold,
your thin blood shifting channels at night
under layers of wool and flannel. The chemicals
do what they can, but they are not magic. There is
no more magic we know of anywhere.

We live very close to the deep well. Already
you have forgotten what we were like together
and you ask me why I am crying.

We have finished eating from a single plate,
you will never sleep in my bed. I cannot
take you with me to the palace.

JEANNE LOHMANN©
San Francisco, California

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Articles

Health Status and National Health Priorities

DOROTHY P. RICE, ScD, *San Francisco, California*

Various measures of the health status of the population of the United States show there is considerable room for improvement. Compared with other industrialized nations, we are spending more for health care but our health is worse. These data form the basis for setting national priorities. Four selected policy issues are discussed, including access to medical care, maternal and child health care, the acquired immunodeficiency syndrome, and long-term care. Examination of these issues leads to the conclusion that universal and affordable health care is the major national health priority, requiring a commitment by the people of the United States and its leaders to develop a viable solution.

(Rice DP: Health status and national health priorities. West J Med 1991 Mar; 154:294-302)

Americans are healthier now than ever before. Death rates for many diseases have declined significantly during the past two decades, and life expectancy has increased. The current health status of the nation is based on decades of progress in sanitation, nutrition, housing, education, income, and medical care. All have contributed to substantial improvements in the health of Americans.

Despite this bright picture, the health status of the nation could be improved:

- Compared with other industrialized nations, US life expectancy at birth in 1986 ranked 20th for men and 15th for women,[1(p117,table21)] and US infant mortality rates ranked 22nd.[1(p116,table20)]
- Infant mortality rates for African Americans are more than double those for whites.
- Cancer death rates continue to increase.
- Accidents are the leading cause of death among children and youth.
- Illicit drug use continues to be a major public health problem.
- The incidence, prevalence, and number of deaths from the acquired immunodeficiency syndrome (AIDS) have been increasing rapidly, and their toll in human and economic terms is enormous.

These are only a few measures of health status that clearly have significant policy implications. In this article I briefly examine these and other aspects of the health of Americans and discuss some major policy issues and national priorities that emerge from these data. These policy issues include access to medical care, maternal and child health care, human immunodeficiency virus (HIV) infection, and long-term care.

Health Status Indicators

Various health status indicators highlight the long-term improvements in health status. Many of the same indicators are also markers of serious health problems and of the existing gaps between subgroups of the population. A brief review of infant and general mortality rates, life expectancy, disease risk factors, medical care use, and expenditures will provide the background for identifying the policy issues and directions for developing national health priorities.

Infant Mortality

Since the early part of this century, tremendous strides were made in infant survival through improved sanitation and socioeconomic conditions, success against infectious diseases, better nutrition, improved access to prenatal care, and advances in lifesaving technology used in neonatal intensive care units. Between 1950 and 1987, the infant mortality rate declined 65%, from 29.2 to 10.1 per 1,000 live births. The overall infant mortality rate, however, masks the large discrepancy between the mortality of white and African-American infants. In 1987 the African-American infant mortality rate was more than twice that for white infants—17.9 versus 8.6 deaths per 1,000 live births, respectively (Table 1).[1] From 1975 to 1987, the ratio of black to white infant mortality actually increased, reflecting a higher than average annual percent decline for white infants (2.7%) than for African-American infants (2.2%).

About two thirds of all infant deaths occur during the neonatal period, the first month of life. The rate of decline in neonatal mortality between 1975 and 1987 was greater for white than for African-American infants, 47% versus 36%. In 1987, the African-American neonatal mortality rate was more than double the rate for white infants.

The racial differences for postneonatal mortality rates, that is, between the 2nd and the 12th month of life, present a similar picture. In 1987 the postneonatal mortality rate for African-American infants was twice that for white infants.

The pronounced gap in the infant mortality rate between white and African-American infants reflects the more than twofold difference in the proportion of low-birth-weight babies (less than 2,500 grams) in the two groups—5.7% compared with 12.7% in 1987.[1(p97,table7)] Some of the factors associated with low birth weights and other major causes of infant deaths are a lack of prenatal care for pregnant women, maternal smoking, alcohol and drug use, age, and the socioeconomic background of the mother.

The United States infant mortality ranks 22nd among other industrialized nations. In 1986 Japan had the lowest infant mortality rate (5.2 deaths per 1,000 live births) and the second lowest perinatal mortality rate (7.3 deaths per 1,000 live births). Finland's perinatal rate was lowest at 6.4 deaths per 1,000 live births. The infant mortality rate for the United

From the Department of Social and Behavioral Sciences, University of California, San Francisco, School of Nursing.
Reprint requests to Dorothy P. Rice, ScD, UCSF School of Nursing, Room N631, San Francisco, CA 94143-0612.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
GDP = gross domestic product
GNP = gross national product
HIV = human immunodeficiency virus
OBRA = Omnibus Budget Reconciliation Act
OECD = Organization for Economic Cooperation and Development

States in 1986 was twice the rate for Japan, and the perinatal mortality rate was almost two thirds higher than that for Finland.

Mortality—All Ages

In 1987, 2.1 million persons died in the United States, a rate of 8.7 per 1,000 population. Because the population has been aging, a more accurate picture of mortality trends is provided by the age-adjusted death rate, which eliminates the distortion associated with changing age composition. Thus, the age-adjusted rate in 1987 was 5.4 per 1,000 population. The crude death rate declined 9.5% while the age-adjusted death rate for the total population declined 36% during the 37-year period, 1950 to 1987 (Table 2).[1] Examination of the trend clearly shows two separate periods: a moderate decline from 1950 to 1970, in which the age-adjusted mortality rate declined at an average annual rate of 0.8%; and a more rapid decline from 1970 to 1987 at 1.7% annually.

Heart disease continues to be the leading cause of death in the United States and, as such, is the predominant influence on total mortality. The age-adjusted heart disease death rate decreased 45% from 1950 to 1987. Some suggested explanations for the decline in heart disease mortality include the decreased prevalence of smoking, improved management of hypertension, healthier life-styles, the decreased dietary intake of saturated fats, more widespread physical activity, improved medical emergency services, and a more widespread use and increased efficacy of coronary care units.

The mortality for malignant neoplasms, or cancer, the second leading cause of death, increased 6% since 1950. The highest rate of increase (210%) occurred in cancer of the respiratory system mainly due to the effects of smoking.

Cerebrovascular disease, or stroke, is the third leading cause of death. From 1950 to 1987, the cerebrovascular age-adjusted mortality rates decreased 66%. Factors related to the rapid decline include expanded hypertension screening programs, improved management and rehabilitation of stroke victims, and effective hypertension therapy.

The mortality rates for accidents and suicides, the fourth and fifth leading causes of death in the United States, have declined since 1970, but they remain high. The death rate from HIV infection was 8.3 per 100,000 persons in 1987; in the year ending May 1990, HIV deaths climbed to 39,203, a rate of 15.4 per 100,000 persons, ranking it among the ten leading causes of death in the United States.[2]

Life Expectancy

Since the turn of the century, more than a quarter century has been added to life expectancy at birth. Improvements in life expectancy early in this century have resulted from the control of acute infectious diseases, primarily by reductions in infant mortality. More recent improvements have been due to declining mortality from chronic diseases in the middle and older ages.

There have been and continue to be marked differences in life expectancy at birth for Americans by sex and race. Women live longer than men, and whites live longer than African Americans. In 1988, white women had the longest life expectancy, 78.9 years, and black men had the shortest, 65.1 years (Table 3).[1] Although improvements in life expectancy have occurred for all race-sex groups, the amount of improvement varies among these groups. Between 1950 and 1988, life expectancy increased 5.6 years for white men, 6.2 years for black men, 6.7 years for white women, and 11.1 years for black women.

Increasing life expectancy and declining death rates have resulted in a rapid growth of the population aged 65 and older. This population group will continue to grow at a rapid rate for the remainder of the 20th century and well into the next century. At the turn of the century, there were only 3.1 million elderly people, 4.0% of the total population.[3] By 1980, the elderly population had grown to 25.7 million persons, representing 11.3% of the total population. Because of the aging of the "baby boomers" born between 1946 and 1965, about one out of five Americans will be 65 years of age or older by the year 2030, and the total number is projected to be 65.6 million, more than doubling in the 50-year period, 1980 to 2030.

Like infant mortality rates, life expectancy in the United States is lower than for many industrialized nations, ranking 20th for men and 15th for women in 1986. Japan had the longest life expectancy of industrialized countries, 75.5 years for men and 81.6 years for women.

Health Status

In addition to mortality rates and life expectancy, various measures can be used to depict the health of the population:

TABLE 1.—*Infant Mortality Rates by Race, United States, Selected Years 1950-1987*†*

Race and Year	Infant Deaths, No./10³ Live Births: Total	Neonatal	Post-neonatal
All Races			
1950	29.2	20.5	8.7
1960	26.0	18.7	7.3
1965	24.7	17.7	7.0
1970	20.0	15.1	4.9
1975	16.1	11.6	4.5
1980	12.6	8.5	4.1
1985	10.6	7.0	3.7
1987	10.1	6.5	3.6
White			
1950	26.8	19.4	7.4
1960	22.9	17.2	5.7
1965	21.5	16.1	5.4
1970	17.8	13.8	4.0
1975	14.2	10.4	3.8
1980	11.0	7.5	3.5
1985	9.3	6.1	3.2
1987	8.6	5.5	3.1
African American			
1950	43.9	27.8	16.1
1960	44.3	27.8	16.5
1965	41.7	26.5	15.2
1970	32.6	22.8	9.9
1975	26.2	18.3	7.9
1980	21.4	14.1	7.3
1985	18.2	12.1	6.1
1987	17.9	11.7	6.1

*From the National Center for Health Statistics.1(p107,table15)

†Infant mortality rate is the number of deaths of infants younger than 1 year per 1,000 live births. Neonatal deaths occur within 28 days of birth; postneonatal deaths occur 28 to 365 days after birth.

persons' perception of their health, limitations in their usual activities, and restricted and bed-disability days. Table 4 summarizes these health status measures by family income.[4] For every measure, health status improves with rising incomes. In 1988, 10% of the noninstitutionalized population reported that their health was fair or poor compared with people their age, with the percent declining from 22% for those with family incomes of under $10,000 a year to 4% for those with incomes of $35,000 or more. About 33 million persons, 14% of the noninstitutionalized population, reported limitations of activity—that is, preschool or school activities, employment, or keeping house—due to chronic diseases. The percent suffering a limitation of activity declines with increasing income: 26% for the lowest income group to 8% for the highest income group. Likewise, the percentage of persons unable to carry on their major activity and of those with restricted activity and bed-disability days also declines with increasing income.[4]

Disease Risk Factors

Various risk factors have been identified to prevent or to control many diseases and promote good health. The growth in knowledge and awareness of the importance of health promotion and disease prevention in reducing unnecessary illness, disability, and deaths in the United States is the basis for a major focus of activity in the Public Health Service. In 1979, consensus among public health authorities was clearly communicated in *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention.* The message was that many major health problems confronting Americans today are rooted in life-style or environmental factors that are amenable to change.[5] Broad national goals for improving the health of American people during the decade of the 1980s were delineated, and 15 areas encompassing 226 specific objectives were identified in which health promotion and disease prevention measures might be expected to achieve further progress through a wide range of public, private, and individual strategies.

A recently published review of the progress made by 1987 on these objectives shows a patchwork of successes, serious failures, and health status areas that fall in between.[1] Four examples of several important failures in progress toward accomplishing the 1990 objectives in which reduced risk factors were identified are listed below:

- High blood pressure control: The control of hypertension is one of the most effective prevention efforts to reduce death rates from heart disease and stroke. The control of high blood pressure, redefined to a measurement of 140/90 mm of mercury or higher, has not been reached by 60% of the population at risk, the objective established for 1990. Area studies estimate that only 24% of persons with hypertension have their blood pressure under control.[6] Although there is some decline in sodium intake, a major risk factor for hypertension, progress is difficult to assess. It is also unlikely that the prevalence of overweight persons can be reduced to 10% of men and 17% of women. From 1976 to 1980, 24.4% of men and 26.7% of women 20 to 74 years of age were overweight.
- Pregnancy and infant health: The progress toward the pregnancy and infant health goals is the most disheartening. The 1990 goals for infant mortality of 9 per 1,000 live births for all races and 12 deaths per 1,000 live African-American infants are unlikely to be met. As shown in Table 1, the infant mortality rate for all races was 10.1 per 1,000 live births and 17.9 for African-American infants in 1987. Rates for low-birth-weight babies, a major risk factor in infant mortality, have had only small declines from 7.1% of all live births in 1978 to 6.9% in 1987. The 1990 objective was set at 5%. The proportion of mothers receiving no prenatal care in the first trimester of pregnancy, the goal for which was set at 10% by 1990, ranged from 21% for whites to about 40% for African Americans, American Indians, and Hispanics in 1987.
- Smoking: Cigarette smoking is the largest single preventable cause of illness and premature death in the United States, amounting to 390,000 deaths each year in the United States. Cigarette smoking is a major risk factor for lung cancer and other cancers, including laryngeal, esophageal, and urinary bladder cancer, for coronary artery disease, chronic obstructive lung disease, some forms of cerebrovascular disease, spontaneous abortion, retarded fetal growth, and fetal or neonatal death.

Although progress has been made in educating the public about many of the adverse health outcomes associated with smoking, 28.8% of adults smoked cigarettes in 1987; the goal is 24.9% by 1990. The proportion of children and youth

TABLE 2.—*Age-Adjusted Death Rates and Percentage Change by Cause of Death, United States, Selected Years 1950 to 1987**

Cause of Death	Deaths, No./10^5 Population 1950	1970	1987	Average Annual Percent Change 1950-1970	1970-1987	Percent Change 1950-1987
Total						
Age-adjusted	840.5	714.3	535.5	−0.8	−1.7	−36.3
Crude	963.8	945.3	872.4	−0.1	−0.5	−9.5
Diseases of heart	307.2	253.6	169.6	−1.0	−2.3	−44.8
Cerebrovascular diseases	88.6	66.3	30.3	−1.4	−4.5	−65.8
Malignant neoplasms	125.3	129.8	132.9	+0.2	+0.1	+6.1
Respiratory system	12.8	28.4	39.7	+4.1	+2.0	+210.2
Prostate†	13.4	14.4	14.9	+0.4	+0.2	+1.1
Breast‡	22.2	23.1	22.9	+0.2	−0.1	+1.0
Accidents	57.5	53.7	34.6	−0.3	−2.6	−39.8
Suicide	23.3	27.4	19.5	+0.8	−1.2	−16.3
HIV infection	...	...	8.3	...	...	...

HIV = human immunodeficiency virus

*Adapted from the National Center for Health Statistics.1(p121,table23)
†Men only.
‡Women only.

aged 12 to 18 years who smoked in 1988 was 12%; the 1990 goal was set at 6%. Knowledge of the adverse effects of smoking during pregnancy is less widespread. In 1985, the percentage of women not aware that smoking during pregnancy increases a woman's chances of having a miscarriage was 26%; of low birth weight, 20%; of stillbirth, 34%; and of premature birth, 30%.

• Alcohol and drug abuse: Alcohol and drug use cause or are associated with deaths due to accidents, homicides, suicides, cirrhosis of the liver, and cancer of certain sites. Their use poses special risks among adolescents, young adults, pregnant women, and the elderly. In 1988 a quarter of adolescents aged 12 to 17 reported using alcohol within the past 30 days. The use of alcohol, marijuana, cocaine, and other illicit drugs has been declining since the late 1970s as awareness of the risks associated with their misuse has been growing. In 1987 about 4.3% and in 1988 about 3.4% of high school seniors reported using cocaine in the past 30 days, compared with 6.7% in 1985 and 6.2% in 1986. These data were collected before the recent increase in crack cocaine use.

A survey of 13 hospitals in 8 cities by the Inspector General of the US Department of Health and Human Services found that 8,974 newborns were treated in 1989 for exposure to crack cocaine. Delivery and hospital care of these infants cost $300 million more than normal delivery and care. At least 100,000 crack babies are estimated to be born annually, at a cost of more than $3 billion for medical care.[7]

• Sexually transmitted diseases: Although the prevalence rates of traditionally recognized sexually transmitted diseases—gonorrhea, nongonococcal urethritis, genital herpes, and syphilis—have been reduced substantially, the scope and complexity of the sexually transmitted disease problem in the United States have expanded at an alarming rate. Infection with HIV, which was unknown when the 1990 objectives were established, has emerged as a major sexually transmitted disease and presents a major health problem in the nation, as will be discussed further.

TABLE 3.—*Life Expectancy at Birth by Race and Sex, United States, Selected Years 1900 to 1988**

Race and Year	Years: Both Sexes	Male	Female
All Races			
1900	47.3	46.3	48.3
1950	68.2	65.6	71.1
1960	69.7	66.6	73.1
1965	70.2	66.8	73.7
1970	70.9	67.1	74.8
1975	72.6	68.8	76.6
1980	73.7	70.0	77.4
1985	74.7	71.2	78.2
1988†	74.9	71.4	78.3
White			
1900	47.6	46.6	48.7
1950	69.1	66.5	72.2
1960	70.6	67.4	74.1
1965	71.0	67.6	74.7
1970	71.7	68.0	75.6
1975	73.4	69.5	77.3
1980	74.4	70.7	78.1
1985	75.3	71.9	78.7
1988†	75.5	72.1	78.9
African American			
1900	33.0	32.5	33.5
1950	60.7	58.9	62.7
1960	63.2	60.7	65.9
1965	64.1	61.1	67.4
1970	64.1	60.0	68.3
1975	66.8	62.4	71.3
1980	68.1	63.8	72.5
1985	69.5	65.3	73.5
1988†	69.5	65.1	73.8

*From the National Center for Health Statistics.1(p106,table14)
†Provisional data.

Use of Medical Services

The use of medical care has an inverse relationship with family income (Table 4). In 1988 noninstitutionalized persons in the lowest income group had 6.6 physician contacts (other than contacts as hospital inpatients); those in the highest income class had 5.3 visits. There were 27.1 million discharges from nonfederal short-stay hospitals in 1988, with a total of 170 million days of care. Persons in the lowest income bracket are almost 2½ times as likely to be admitted to hospital as those in the highest income bracket. The length of stay for the lowest income group was 1.3 times that of the highest income bracket.[5] It is clear that the health status of persons in the lowest income group is much worse than for those with higher incomes, and their medical care use is significantly higher.

Medical care expenditures. During 1960 to 1988, medical care spending increased from $27 billion to $540 billion while its share of the gross national product (GNP) more than doubled, rising from 5.3% to 11.1% (Table 5). Health spending in 1988 amounted to $2,124 per capita, rising from $143 in 1960.[8]

The factors associated with the rise in health care spending are multiple and complex, including the growth in private

TABLE 4.—*Health Status and Utilization Measures by Family Income, United States, 1988**

Measure	All Persons	Family Income: Under $10,000	$10,000 to $19,999	$20,000 to $34,999	$35,000 or More
Health Status					
Percent feeling fair or poor	9.9	22.1	14.3	7.4	4.0
Percent limited in activity†	13.7	26.0	18.1	11.5	7.9
Percent unable to carry on major activity†	4.0	9.1	5.9	2.9	1.5
Restricted-activity days per person†	14.7	26.6	17.8	12.3	9.7
Bed-disability days per person†	6.3	12.2	7.9	4.9	3.8
Utilization					
Physician contacts per person, No.	5.4	6.6	5.6	5.2	5.3
Percent seeing doctor in past year, %	76.7	78.0	74.9	76.3	78.9
Short-stay hospital discharges per 100 persons, No.	11.2	18.7	13.4	10.1	7.7
Average length of stay in short-stay hospitals, days	6.3	6.9	6.3	5.8	5.4

*From the National Center for Health Statistics.4
†Due to chronic conditions.

health insurance and prepayment plans; increased public support of medical care for the aged, disabled, and poor; changing third-party reimbursement methods; increasing population and a rising proportion of elderly requiring more medical care; a shift from the care of acute to more expensive long-term illnesses; the improvement and growth of high-cost technology; higher wages and salary costs in the health care industry; and growth in the supply of health care professionals and facilities. The growing burden on the economy of medical care spending results from all of the above factors as well as higher medical care prices relative to general prices and a slower rate of growth in the general economy compared with continued growth in the health sector. Thus, in the period 1960 to 1988, the GNP grew 9.5 times and health expenditures grew 20 times.

The major portion of health care expenses has in the past been borne by the private sector. In 1960, 27% of total health care spending was paid by private health insurance and philanthropy, 49% of the total comprised direct out-of-pocket payments, and public spending accounted for 25%. The implementation of Medicare and Medicaid, together with increasing coverage of private health insurance, altered these relationships. By 1988 the government's portion rose to 42% of the total. Private health insurance and philanthropy covered 37%, further reducing direct private payments to 21% of the health care bill compared with 49% in 1960. The rise in third-party payments tends to reduce the financial burden of serious illness and patients' concern about the cost of care received and removes the restraining influences from physicians to admit patients to hospitals and use high-cost technologies.

The aged represented about 12% of the population in 1987, but because they tend to be sicker than younger people and use more health care services, they accounted for 36% of expenditures for personal health care.[9] Per capita spending for elderly persons amounted to $5,360 compared with $745 for persons younger than 19 years and $1,535 for adults aged 19 to 64. Almost two thirds of the expenditures for the aged in 1987 (63%) came from public programs, and the remaining 37% came from private payments, out-of-pocket payments, and private insurance, including Medigap policies.

Elderly people approaching death have high expenditures for medical care. In 1982, the top 5% of these decedents accounted for 27% of Medicare reimbursements.[10] Incurring high medical costs at the end of life is not a new phenomenon, and available data do not support the assumption that high medical expenses at the end of life are due largely to aggressive, intensive treatment of patients who are moribund. The data suggest that most sick people who die are given the medical care generally provided to the sick, and sick care is expensive.[11-13]

A study of health care spending in 24 countries in the Organization for Economic Cooperation and Development (OECD) shows that per capita health expenditures averaged $870 in US dollars, ranging from $140 in Turkey to $1,926 in the United States.[14] US spending exceeded that of Canada by 41%, France by 85%, Germany by 87%, Japan by 131%, Italy by 152%, and the United Kingdom by 171%.

The health share of the gross domestic product (GDP), a better measure for international comparisons than the GNP, ranged from 3.6% in Turkey to 11.1% in the United States. While the health share of the GDP in this country has increased from 10.5% in 1983 to 11.1% in 1986, most of the other six major OECD countries have exhibited stability in their percentages of GDP devoted to health over this three-year period.

Major Policy Issues and National Priorities

The foregoing health status and expenditure data have important policy implications and form the basis for setting national priorities and action. Only a selected few policy issues will be briefly highlighted, including access to medical care, maternal and child health care, AIDS, and long-term care.

Access to Medical Care

Since the enactment of Medicare and Medicaid in 1965, impressive strides have been made in ensuring improved access to the benefits of the health care system for many Americans. More people attained regular access to health services, and a backlog of long-neglected needs, especially among the elderly and the poor, was specifically addressed. Medicaid was successful in improving access to medical services for the population it covers. The poor, however, tend to be sicker than the nonpoor, so that the higher medical care use rates among the poor by the mid-1970s did not necessarily indicate that they received more care given a similar health status. After adjustment for health status, poor persons who reported their health as fair or poor had substantially fewer visits than those in the highest income groups.[15] In addition, those poor not covered by Medicaid continued to lag well behind others in the use of services.[16]

Data from the 1986 Robert Wood Johnson National Access Survey showed a deterioration in access to medical care for the nation's poor, minorities, and uninsured between 1982 and 1986. Physician visits for the low-income group in poorer health declined by 8% compared with an increase of 42% for the nonpoor in similar health status, widening a gap

TABLE 5.—*Gross National Product (GNP) and National Health Expenditures by Source of Funds, Selected Years, 1960 to 1988**

		National Health Expenditures						
		Total			*Private Funds*		*Public Funds*	
Year	*GNP, $ × 10^{12}*	*Amount, $ × 10^{12}*	*Per Capita, $*	*Percent of GNP*	*Amount, $ × 10^{12}*	*Percent of Total*	*Amount, $ × 10^{12}*	*Percent of Total*
1960	515	27.1	143	5.3	20.5	75.5	6.7	24.5
1965	705	41.6	204	5.9	31.3	75.3	10.3	24.7
1970	1,015	74.4	346	7.3	46.7	62.8	27.7	37.2
1975	1,598	132.9	592	8.3	77.8	58.5	55.1	41.5
1980	2,732	249.1	1,059	9.1	143.9	57.8	105.2	42.2
1985	4,015	420.1	1,700	10.5	245.2	58.4	174.9	41.6
1988	4,881	539.9	2,124	11.1	312.4	57.9	227.5	42.1

*From the Health Care Financing Administration.[8]

that had almost disappeared. For the elderly poor, physician visits declined 20% during this four-year period. The gap in the number of physician visits among ethnic groups also widened, and there was evidence of an underuse of medical care in 1986 by low-income persons with chronic and serious illnesses.[17]

One of the primary factors in determining access to health care is insurance coverage through both public and private programs. The estimated number of currently uninsured persons younger than 65 ranges between 31 and 37 million.[18,19] Whatever the precise number of uninsured, two facts are clear: the number and percent of the population without health insurance have grown in the past few years, and access to care is more difficult for these people. The 1986 National Access Survey found that uninsured persons were twice as likely as the insured to be without a regular source of medical care. They had 27% fewer ambulatory visits and a slightly higher rate of medical emergencies.[2a]

The National Medical Expenditure Survey reported that 37 million persons, 15.5% of the total population, had no private health insurance coverage in 1987 (Table 6).[21] Persons aged 19 to 24 are least likely to be insured—three out of ten persons in this age group have no public or private coverage. The disparities between the white and minority populations are high—12% of whites, 22% of African Americans, and 32% of Hispanics have no public or private health insurance coverage. The same survey reported that single, divorced, and separated persons are also at high risk for no insurance coverage. Part-time and self-employed persons, workers employed in industries characterized by seasonal employment—agriculture, construction, sales, repair, entertainment, and personal services—were less likely to have employment-related insurance and were more likely to be uninsured. Because the uninsured lack ready access to medical care, these data clearly show that impaired access goes beyond the poor and the unemployed population. Many employed persons in low-paying and seasonal occupations and who work for small businesses also are uninsured. About half of the uninsured are employed either all or part of the year. When their dependents are included, the employed uninsured account for 70% to 75% of the uninsured populations.[22]

In addition to those without any private health insurance protection or coverage under Medicaid or Medicare, many other Americans are underinsured. One study analyzed the 1977 National Medical Care Expenditures Survey and concluded that about 27% of the population, 50.7 million persons in 1977, had inadequate or no insurance coverage.[23] With the continued rise in health care expenditures, the number and proportion of the population without adequate health insurance protection are likely to be higher now. The shift of the labor force from union to nonunion, from full-time to part-time, and from high- to low-wage jobs contributes to the rise in the numbers of uninsured and underinsured working persons.

The access issue is about the social obligation of government to provide care for low-income people or those who are otherwise uninsured. Although many uninsured persons are poor, they do not qualify for Medicaid because they are not categorically eligible or have incomes above the Medicaid cutoff level for the states in which they reside. Medicaid initially covered more than 60% of the poor but now only covers about 45%.[24]

The recent focus of commissions, policy analysts, states, hospital and health professional associations, and private foundations has been on the uninsured population. The inability of large public hospitals to shift the cost of uncompensated services to patients with insurance has stimulated discussion of this issue. State governments are concerned about rising Medicaid costs. As of February 1988, 15 states had enacted laws establishing health insurance risk pools for people who have been rejected for coverage by at least one insurance company.[25]

The issue of how to provide care to uninsured and underinsured Americans lies at the heart of the access-to-health-care issue. A consensus appears to be emerging among diverse groups that the United States should extend health care to those who do not have access to it. The question is how best to provide and finance such care.

Maternal and Child Health Care

Comprehensive prenatal care results in healthier babies, prevents human suffering, and saves money by reducing the need for high-cost hospital care of low-birth-weight babies.

TABLE 6.—*Health Insurance Coverage by Selected Characteristics: Percent with Public, Private, Employment-Related, and No Coverage, 1987*†*

		Type of Health Insurance			
Population Characteristics	*Population, × 10³*	*All Private Coverage, %*	*Employment-Related Private Coverage, %*	*Only Public Coverage, %*	*None, %*
Total	237,890	74.5	64.3	10.0	15.5
Age, years					
< 6	21,631	67.5	62.5	15.8	16.7
6 to 18	45,475	71.8	67.8	11.3	16.9
19 to 24	22,675	63.3	55.2	6.5	30.2
25 to 54	98,155	78.8	73.2	5.5	15.7
55 to 64	22,046	79.0	65.2	7.6	13.4
≥ 65	27,909	74.7	35.4	24.4	0.9
Sex					
Male	115,148	75.1	65.9	8.3	16.6
Female	122,743	74.0	62.8	11.7	14.3
Racial/ethnic background					
White	182,794	80.8	69.1	6.8	12.4
African American	28,356	52.9	48.5	25.1	22.0
Hispanic	18,752	50.1	45.9	18.3	31.5

*From the National Center for Health Services Research and Health Care Technology Assessment.[21]
†Numbers may not add to total due to rounding.

The Office of Technology Assessment estimates that the annual cost of neonatal intensive care in the United States is more than $1.5 billion.[26] A 1985 Institute of Medicine study found overwhelming evidence that prenatal care reduces the incidence of low birth weights.[27] There is also evidence that access to prenatal care has deteriorated in the past few years.[1]

State Medicaid programs are concerned because women living in poverty have a higher risk of having low-birthweight babies with complex and costly medical problems. Many low-income women do not qualify for Medicaid protection, are not covered by private health insurance, and cannot afford prenatal care. They do not get prenatal care, and their babies are delivered as hospital charity cases, contributing to the problem of hospital uncompensated care. The rate of low birth weight among infants born to women who receive no prenatal care is almost three times that of the general population.

The Omnibus Budget Reconciliation Act (OBRA) of 1989 had several important Medicaid amendments that expanded health coverage for low-income women and children. Under OBRA-1986, states were required to provide Medicaid to pregnant women and infants younger than 1 year whose incomes are at or below 100% of the federal poverty level. The 1989 version required states to extend coverage to pregnant women and children up to age 6 with incomes at or below 133% of the federal poverty income level ($13,380 for a family of three). The Congressional Budget Office estimated that this provision increased by 852,000 the number of children who would participate in Medicaid over the next three years.

The 1989 OBRA also specifically sought to assure that payment levels for obstetric and pediatric services were sufficient to enlist enough providers so that covered services would be available to Medicaid recipients to at least the extent that such services are available to the general population. In addition, the new amendments attempted to improve access to the Early and Periodic Screening, Diagnostic, and Treatment program (EPSDT), a part of Medicaid that provides preventive care and treatment of low-income children; and responded more fully to the health care needs of children by allowing more checkups when an illness or condition is suspected. An important change was a new requirement that states provide any medically necessary follow-up or treatment service that is reimbursable under Medicaid, whether or not the service is included in the state Medicaid plan.

Medicaid income eligibility criteria remain at the discretion of the states. Although these recent Medicaid changes are important, are they sufficient to reach all pregnant women and children? Medicaid still reaches only the very poor; the working poor are still at risk. Of major concern to policy makers is the number of children without any form of insurance coverage—11.3 million children younger than 18 years. It is time that the federal government assumes responsibility for guaranteeing that high-quality, comprehensive, and preventive maternal and child health care be available and accessible to all citizens of the United States needing such services.

Acquired Immunodeficiency Syndrome

Any examination of the health status of the nation and the implications for governmental priorities and actions would be incomplete without discussing HIV-related disease and AIDS, labeled by public health experts as a "world-class epidemic."[28] Between 1981 and the end of May 1990, AIDS was diagnosed in 136,204 persons and more than three fifths died. The World Health Organization estimates that 6 to 8 million people worldwide have been infected with the HIV virus and 15 to 20 million people will be infected by the turn of the century.

According to the Institute of Medicine, 1.5 million Americans may be infected with the human retrovirus HIV.[29(p85)] The latency period between infection and an AIDS diagnosis averages four or more years in adults. Consequently, most persons in whom AIDS will develop in the next few years will be those who are already infected. As the epidemic enters its second decade in the United States, the trend is toward infection of an increasing number of heterosexual persons, especially intravenous drug users and their sexual partners, minorities, children, and the poor. The Public Health Service warns that by the end of 1992, more than 360,000 Americans will have received a diagnosis of AIDS, and more than 260,000 will have died.[30] Overall, the number of reported cases of AIDS in the United States continues to increase, but the encouraging news is that the increase is lower than in past years. This changing trend is attributed to three factors: changes in behavior among those at highest risk; AIDS case reporting may now be less complete or more delayed; and new therapies that slow the development of severe illness may lead to fewer cases of AIDS being diagnosed.[31]

The acquired immunodeficiency syndrome clearly is placing an increasing burden on the health care delivery system. In addition to expenditures for medical care and nonpersonal services (direct costs), the value of lost output due to the cessation or reduction of productivity by morbidity and mortality (indirect costs) should also be considered. Scitovsky and Rice estimated the annual direct and indirect costs of AIDS in 1985, 1986, and 1991.[32] According to the authors' best estimates, direct costs, including research and nonpersonal services, will rise from $1.7 billion in 1986 to $10.9 billion in 1991 and indirect costs are estimated to rise from $7 billion in 1986 to $55.6 billion in 1991.

More recent national estimates of spending costs of treating AIDS patients amount to $3.3 billion in 1989, and by 1993 the cost will rise to $7.9 billion.[33] The introduction of AIDS drugs such as zidovudine (AZT) has been promising in increasing the life span of AIDS patients. The lifetime medical cost of treating a person with AIDS is estimated at $75,000 per case, assuming an average survival of 15 months from the time of diagnosis.

The federal government spent $2.9 billion in 1990 on research, care, and public health programs. The responsibility for paying for AIDS care, however, is shifting to the state and local governments. About 5% of the nation's urban public hospitals are treating more than 50% of persons with AIDS, and a quarter of all AIDS patients have no form of insurance, private or public.[34]

Long-term Care

Persons who have lost some capacity for self-care because of chronic disease or who suffer disabling physical or mental conditions require a wide range of social, personal, and supportive services in addition to medical care. With the growing number of chronically ill elderly and disabled adults, increasing consideration is being given to alternatives to providing long-term care services and to preventing the need for institutionalization. A wide range of options has

been discussed and initiated to eliminate the fragmentation of services and to promote a continuum of care, including social health maintenance organizations; revamping reimbursement incentives to institutional providers to improve quality of care; and changing program incentives from medicalized solutions to social-health support services, such as hospice, home health, day-care centers, residential care homes, rehabilitation centers, and case management. Many of these are being tested under Medicare and Medicaid waivers and state experiments. Such innovative approaches are needed to meet the growing long-term care needs of the elderly and to promote a continuum of care in a cost-effective manner.

The Pepper Commission recommended a two-pronged approach to long-term care[35]:

- Home and community-based care would be available to the severely disabled of all ages, who would be entitled to an array of benefits, including home health care, personal care and homemaker chore services, adult day care, and respite care. Beneficiaries would pay 20% of the costs, and the government would provide subsidies for those with incomes lower than twice the poverty level.
- Nursing home care, including long-term custodial or skilled care, would be provided for as long as needed. For the first three months, beneficiaries would pay 20% of the costs, with subsidies provided for those with incomes lower than twice the poverty level. After three months, the government would pay all costs for those with assets below $30,000 for individuals and $60,000 for couples, not including a house. Nearly two thirds of the elderly are estimated to fall into this group.

These long-term care provisions would cost the federal government $44.8 billion when fully implemented. Objections and concerns have been raised because the Commission failed to specify a method of financing.

While Congress is seeking ways to cover the cost of nursing home care, home health care, and other long-term care services, nearly 40 states have taken steps to ensure that some of long-term care private insurance is available to the elderly (American Association of Retired Persons, *News Bulletin*, 1987, vol 8). Included are incentives for the purchase of long-term care policies by reducing the premium tax that insurers pay for such coverage, setting standards for private policies, or mandating coverage under health insurance policies. Private insurance is not a viable option for everyone and does not preclude the need for a much larger public sector role. Whether Medicare is expanded or a new long-term care program is created, a comprehensive solution will be expensive. A public commitment to a broad-based revenue source is needed to adequately cover long-term care services.

Conclusion

With the continued rise in medical care spending, we are forced to ask whether we are getting full value for our investment in health. We can assess the value received for our health care dollar on a macro basis by comparing our health status and health care spending with those of other nations. Americans spend 2.2 times as much per capita for health care as the average for 21 OECD countries. Yet, we rank 22nd in infant mortality rates, 20th in life expectancy for men, and 15th for women. Japan has half our infant mortality rate, the longest life expectancy at birth, and its per capita expenditure for health is less than half of ours.

Access to care is the key indicator of the availability of services to the general population. All of the OECD nations, including our northern neighbor, Canada, have national health insurance or a national health service making medical care available to all their citizens. In our country, from 31 to 37 million Americans are uninsured and are denied basic medical care.

It is not difficult to conclude that the vast expenditures for medical care in this country are providing neither universal access nor the higher health status that many other developed countries enjoy for a proportionately smaller expenditure. Nor is it difficult to conclude that providing universal and affordable health care is the major health priority, requiring a commitment by the people of the United States and its leaders.

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Safety Belts and Public Health
The Role of Medical Practitioners

KENNETH W. KIZER, MD, MPH, *and* ROGER B. TRENT, PhD, *Sacramento, California*

This is one of a series of articles from western state public health departments.

Medical practitioners have helped the public become aware of the importance of health-promoting life-style changes such as getting more exercise and abstaining from smoking. They can likewise help their patients protect themselves from the threat of automobile crash injury. Safety belt use remains too low, and increased use offers unusual potential for averting death and disability. Various characteristics associated with a failure to use safety belts can be used to help identify patients at high risk of traffic injury. These include male sex, persons who are ethnic minorities, young people, poor people, those with low educational levels, and persons with negative attitudes to seat belt use. Various methods and resources are available to help practitioners provide appropriate safety belt advice to patients, although the specific resources available vary from place to place. At a minimum, patients need to be told that a proper use of occupant protection can at least double the chances of avoiding death or severe injury in an automobile crash.

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Physicians and other medical practitioners influence their patients in many ways. Their role in communicating the importance of proper diet and avoiding harmful practices such as smoking and immoderate drinking is well known. Medical professionals, however, often do not recognize or act on opportunities to help their patients avoid injury by wearing safety belts.

Practitioners who routinely encourage their patients to eat better, stop smoking, and get more exercise often do not tell them to buckle their safety belts. It seems that seat belt use is often viewed as a safety issue rather than a health issue, or more as the proper concern of law enforcement rather than medical personnel. Or perhaps health care practitioners may not know where to get appropriate safety belt promotion materials. Whatever the reason, this situation needs to change. Physicians should actively and vigorously promote the wearing of safety belts, which is crucial to controlling the burden of highway-related morbidity and mortality.

Safety Belts, Injury, and Death

The magnitude and public health significance of injuries are often not appreciated, even though injuries have a high incidence and injury disability has high prevalence. In 1986, one in four Americans suffered an injury serious enough to require medical treatment. Because of injuries, 94,000 Americans lost their lives and almost 9,000,000 were disabled beyond the day the injury occurred.[1]

The injury statistics are impressive, but they fail to tell the whole story: Injury most often strikes children and adults in their prime. It is the leading cause of death among Americans aged 45 and younger (Figure 1),[2] with injury deaths highest among persons in their 20s. While great progress has been made in the prevention and treatment of most chronic illnesses and many virulent infectious diseases, considerably less progress has been made in controlling injury.

Of all the causes of serious injury, the most frequent and most severe are motor vehicle accidents. Despite impressive reductions in traffic-related morbidity and mortality, these injuries still kill more than 47,000 persons each year and permanently disable 1,800,000.[1] Motor vehicle accidents are the number one cause of fatal injury at work[1] and the leading cause of spinal cord injury and traumatic brain damage.[3,4]

As are injuries in general, traffic accidents are a scourge of youth. About one in three deaths due to motor vehicle accidents involves someone between ages 15 and 25.[1] One way to measure the extent to which a cause of death affects younger people is to count the average years of life lost by each fatality, assuming that the victims would have lived to age 65. Motor vehicle accidents are the leading source of potential life lost in the United States.[5] In California, the prominence of traffic-related injury as a cause of injury death, particularly of young people, is vividly illustrated in Figure 2.[2]

The National Highway Traffic Safety Administration (NHTSA) and state and local agencies have made great strides in making driving safer through improved road design, better auto crashworthiness, more stringent traffic safety laws, the development of air bags, improved traffic law enforcement, and lower speed limits. Yet the motor vehicle accident toll remains unacceptably high. A greater use of safety belts offers an easy and effective way to prevent many severe injuries and deaths.

After reviewing many effectiveness studies, the NHTSA has concluded that a belted motorist's chances of dying or suffering a serious injury are about half those of an unbelted motorist.[6] Belted motorists are also about two-thirds less likely to be admitted to a hospital for injuries from a traffic crash.[7] Child safety seats reduce both death and injury by two thirds.[8] This is impressive prophylaxis.

From the California Department of Health Services, Sacramento, California.
Reprint requests to Kenneth W. Kizer, MD, MPH, Director, California Dept of Health Services, 714 P St, Rm 1253, Sacramento, CA 95814

Safety belt effectiveness is more widely recognized today than ever before, and usage nationally has risen over time. Some portion of the increase comes from state laws requiring motorists to buckle up, but it has also increased independent of laws. In California, usage jumped from 18% to 47% on passage of a safety belt requirement. Although almost two thirds of California motorists now wear safety belts,[9] this proportion is still too small.

The US Surgeon General has noted that the increasing use of safety belts and child safety seats has great potential for improving the public health.[10] Many health and medical organizations have cooperated with the NHTSA in promoting occupant protection.[11] It has been estimated that 100% belt use would avert 12,000 to 15,000 deaths in the United States each year.[6] Insufficient use of safety belts is clearly a major public health problem.

In recognition of this problem, the state of California, through the California Highway Patrol, established the California Safety Belt Task Force in 1989. The goal of the task force was to increase safety belt use to 70% of drivers by the end of 1990. The task force includes a cross section of federal, state, and local agencies representing health, law enforcement, safety, education, and the media, whose coordinated efforts are aimed at increasing enforcement of and compliance with California's safety belt use laws. Because the wearing of safety belts is such an important public health issue, the California Department of Health Services played an active role in the effort. Part of that role involved efforts to raise the position of safety belt use on the public health agenda and to stimulate medical practitioners to advise patients to wear safety belts just as they advise them to develop other health-promoting habits.

Barriers to Safety Belt Use

If health care practitioners are to be effective in advising patients to wear safety belts, they must be able to identify

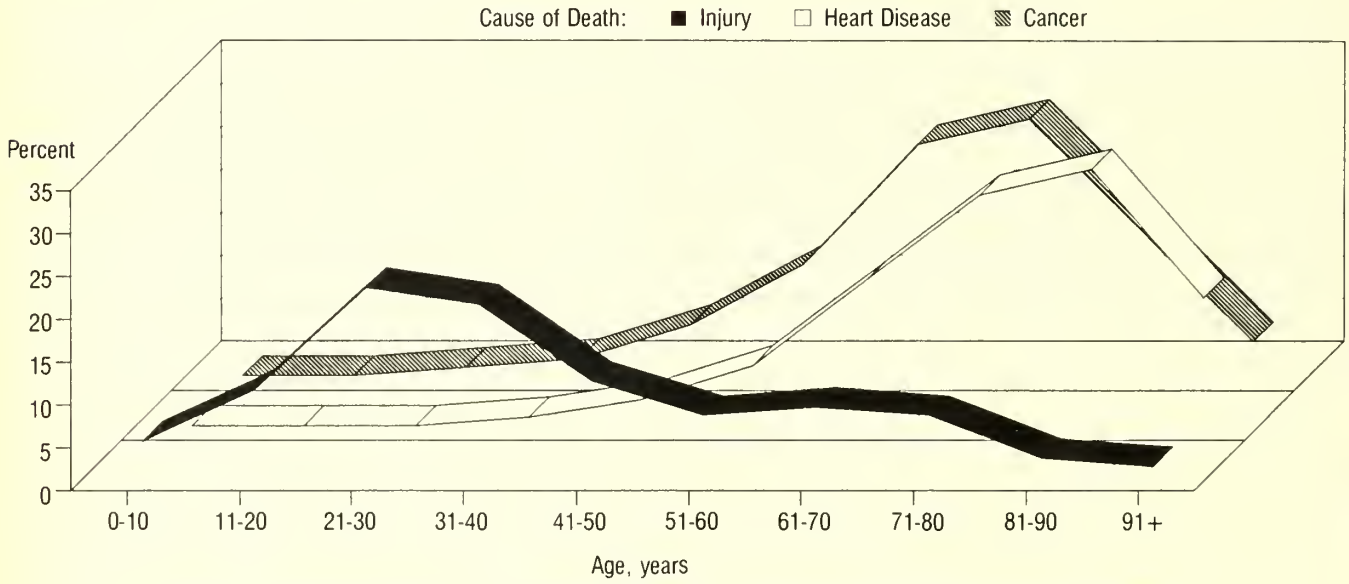

Figure 1.—The graph shows major causes of death according to age group (from Vital Statistics of California, 1988[2]).

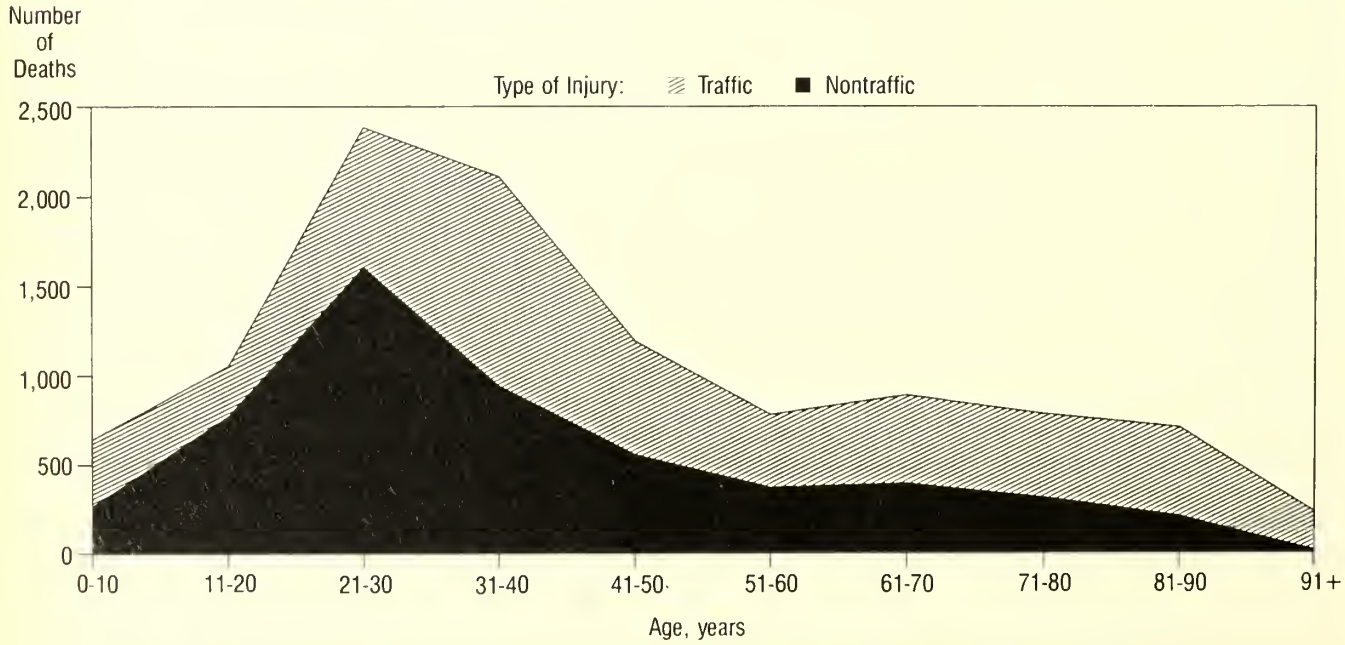

Figure 2.—Shown here are causes of injury death according to age group (from Vital Statistics of California, 1988[2]).

those persons least likely to use them so that promotion efforts can be specifically targeted at least to these patients. In this regard, studies have identified principal risk factors for the nonuse of safety belts as youth, male sex, minority ethnicity, a low level of education, and poverty.[12] An additional and powerful factor is a negative attitude toward belt use.[13]

Patients younger than 25 years, and especially male patients, are at high risk for having an injury from a motor vehicle accident, and safety belt use is consistently low in this group.[14] The typical feelings of invulnerability and immortality and the associated risk taking in this group are well recognized.[15] Therefore, pediatricians, family practitioners, emergency physicians, and others providing primary care should take advantage of the opportunity to establish safety belt use habits among preadolescent patients that may carry over into the years when they begin to drive.

Research has shown that some minority groups (such as African Americans and Hispanics) have low rates of safety belt use. Physicians should make special efforts to ensure that minority and recently immigrated patients are asked about their safety belt use and urged to wear them in a language they feel comfortable with. Non-English-language safety belt promotion materials are increasingly available.

Poverty and low education level are associated with poor health protection habits in general and with lower safety belt use in particular. Medical staff should see to it that poor patients are strongly urged to acquire the safety belt habit. Low-income patients may find it difficult to afford a proper infant car seat, and practitioners should try to put their less affluent patients in touch with groups that loan such devices. Patients whose children have outgrown safety seats may also be a source of free or inexpensive car seats. The promotion of infant car seats by physicians and nurses has been shown to be effective in increasing their use.[16,17]

Many persons justify their not wearing safety belts by inaccurate beliefs about their effectiveness.[18] Thus, safety belt myths are a barrier to use. Medical practitioners are in a unique position of authority to debunk such myths. When they strongly and consistently rally behind a health promotion issue—as they have done on smoking cessation—myths tend to dissipate and a changed public consciousness occurs. Moreover, many research studies have found that safety belt use is correlated with other healthy life-style practices.

Surmounting the Barriers

Medical practitioners require practical communication methods, appropriate resources, and effective messages promoting the use of safety belts. Although no simple packaged program can be applied to all circumstances and patient populations, useful approaches can be outlined. Practitioners can then adopt the one that fits their style of practice and available local opportunities.

A practical communication method is one that is integrated into clinicians' daily contact with patients. For example, practitioners who use a health-risk appraisal to advise patients are presented with an opportunity to discuss the role of safety belts in health maintenance. Questions on safety belt and infant car seat use can be built into health history and checkup forms so that this information—and a cue to discuss the importance of safety belts—becomes as routine as similar information on tobacco and alcohol use. In addition, patients can be exposed more or less automatically to safety belt facts through pamphlets, posters, and even videotaped messages in waiting rooms.

More aggressive communication methods have to be used to reach one group at especially high risk: teenaged drivers. Many young drivers have little contact with medical practitioners. They can be reached through safety belt programs presented in schools, youth clubs, athletic associations, and community organizations. In some areas, "speakers' bureaus" maintain lists of experts who make themselves available to speak on safety belts. Speakers' bureaus value medical practitioners as speakers because of their authority in matters of health and safety. Community outreach programs are perhaps the best way to deliver the safety belt message to teenaged drivers, and such programs have the advantage of reaching many high-risk drivers at once.

Where can medical practitioners get appropriate instructional resources for safety belt education, such as pamphlets, posters, and videotapes? Substantial variation exists in what is available locally, but in most places one or more of the following organizations will either have materials or be knowledgeable about other local programs and resources: the local office of highway patrol or state police, the Ameri-

If you frequently travel in a car—whether you are a good driver or not—sooner or later you are likely to experience a crash serious enough to cause injury or death. No matter what you may have heard,

WEARING A SAFETY BELT
DOUBLES
YOUR CHANCES OF SURVIVING A CAR CRASH

Belted motorists are also two-thirds less likely to be admitted to a hospital for injuries from a traffic crash.

In the event of a crash, you cannot brace yourself with your arms. For example, to do so in a 30-mile-per-hour crash is equivalent to catching a 300-lb bag of cement dropped from a second-story window.

Babies and small children should be placed in child safety seats. If they are held in an adult's arms, they are likely to be crushed against the dash or thrown out of the car if a crash occurs. Child safety seats reduce the risk of death and serious injury by two thirds.

Remember also that most motorists who are "thrown clear" from a traffic accident end up dead or severely injured. In case of fire or submersion, you are more likely to survive if you are belted so that you remain conscious.

For your health, and the safety of your passengers, don't start the engine until everyone is buckled up.

Figure 3.—This is a suggested sign that could be used to promote the use of safety belts.

can Red Cross, the local medical society, the local city or county health department, and the American Automobile Association. On the state level, there is often a seat belt coalition dedicated to increasing safety belt use statewide. Another excellent source is the state office of traffic (or highway) safety. This office serves as a resource center and link between the NHTSA and local traffic safety programs. The state office of traffic safety can make available an array of written and audiovisual supplies, often in languages other than English. Professionally prepared educational materials are a useful source of many appropriate messages on the value of safety belts.

At a minimum, patients who do not wear seat belts need to hear the following message from their physician or other health practitioner: *No matter what you've heard, wearing a safety belt doubles your chances of surviving a car crash.* This message should be delivered orally and otherwise prominently displayed. In addition to this message, practitioners should be ready to combat other myths with information such as the following:

- Persons who frequently travel in cars—whether they are good drivers or not—sooner or later are likely to experience a crash serious enough to cause injury or death.
- In the event of a crash, persons cannot brace themselves with their arms; to do so in a 30-mile-per-hour crash is equivalent to catching a 300-lb bag of cement dropped from a second-story window.
- Children held in an adult's arms are likely to be crushed against the dash or thrown out of the car if a crash occurs.
- The vast majority of motorists who are "thrown clear" end up severely injured or dead.
- In case of fire or submersion, persons are most likely to survive if they are belted so that they remain conscious.

A poster, placard, or other appropriate sign stating the above, such as shown in Figure 3, should be displayed in patient waiting rooms and other visible areas. This message should also be prominently posted in every emergency department waiting area in English and other languages relevant to the patient population served by the hospital.

Comment

In a recent comprehensive literature review, Sleet cited studies showing that 62% of physicians regard safety belt use as an important preventive health behavior and that safety belt promotion messages are most effective when linked to other preventive health practices.[19] Medical professionals are in an excellent position to promote behavior among patients that could help prevent disability and death. Considering that safety belt use is important to almost all patients, is extremely effective, costs little, and entails only minor behavioral changes, promoting the use of auto safety belts presents the medical profession with one of its best opportunities to improve public health and save lives. All medical practitioners are urged to use their voices of authority to promote safety belt use when counseling their patients.

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Conferences and Reviews

A 49-Year-Old Man With Aseptic Meningitis and Multiple Cranial Neuropathies

JOHN C. MAZZIOTTA, MD, PhD; HIDEO ITABASHI, MD; CARL ORFUSS, MD; ANDREW CHARLES, MD; *and* ROBERT COLLINS, MD, *Los Angeles, California*

CARL ORFUSS, MD*: A 49-year-old businessman was admitted to the hospital on June 12, 1989, following a generalized tonic-clonic seizure. The patient had been in good health until five months before admission when double vision developed. He was seen by a neurologist who diagnosed an isolated lesion of the left sixth nerve. No other neurologic abnormalities were noted. A lumbar puncture revealed normal cerebrospinal fluid (CSF) pressure, slightly increased protein levels, no cells, and no reactions on a VDRL test or for cryptococcal antigen, bacterial, fungal, and tuberculous cultures (Table 1). A magnetic resonance imaging (MRI) scan of the head was unremarkable.

A month later, the patient had weakness of the left side of his face, a hoarse voice, and difficulty with balance. He was unable to wrinkle his left forehead or close his left eye tightly. His voice had a slightly nasal quality, and he described occasional difficulty swallowing. Tandem gait was slightly abnormal. A second lumbar puncture revealed normal CSF pressure, a protein concentration of 4.23 grams per liter (423 mg per dl), a glucose level of 1.7 mmol per liter (31 mg per dl), 0.18 monocytes, and 0.01 neutrophils (Table 1). Cytology was normal, and cultures were negative for pathogens. An MRI scan of the head was again normal.

Over the ensuing months, the patient had a progressive 18-kg (40-lb) weight loss. During this time, he reported a possible tick bite a month before the first neurologic symptoms began, accompanied by an evanescent rash. Serology testing for Lyme disease using the enzyme-linked immunosorbent assay (ELISA) with immunoglobulin (Ig) M and G and indirect fluorescent antibody titer for *Borrelia* species was negative. Despite the negative results, he was treated for two weeks with ceftriaxone and amoxicillin plus probenecid.

The patient was an investment counselor who indulged in mild social drinking, had a 50- to 60-pack-year smoking history, and used no medicines or drugs. He had not traveled outside the United States.

On the day of admission, after a generalized tonic-clonic seizure, a regimen of phenytoin (Dilantin) was started. Papilledema was present, and mild dilation of the lateral ventricles was observed on a computed tomographic (CT) scan. A ventricular catheter was placed.

On examination, the patient was cachectic and lethargic but easily arousable. He answered questions slowly but usually accurately. His voice had a nasal quality. There were pooled secretions in the pharynx, and he was unable to cough or swallow. He was able to banter and smile in conversations, however, and could define complex terms such as "junk bond." He exhibited mild confusion with regard to dates. He was able to recall three items after five minutes. There was some mild confusion to commands to perform sequential motor tasks.

Muscle rigidity and pain were present on flexion of the neck, but there was no pain on percussion of the spine. Flexor tendons of the neck were weak. Examination of cranial nerve function revealed a normal ability to read in the right eye but the ability only to count fingers on the left. Visual fields were full. There was bilateral mild papilledema. Light reflex was direct and consensual on the right but absent on the left. Extraocular movements were absent on the left. The right eye showed incomplete abduction and good downward gaze but no other movements. The corneal reflex was absent on the left. No movement of the left facial musculature was evident on command. There was decreased appreciation of a ticking watch in the left ear. The patient was unable to elevate the left side of the palate. The tongue showed normal bulk and movement bilaterally.

Examination of his muscles revealed generalized, symmetric, mild to moderate wasting. Motor tone was normal. Muscle strength was mildly decreased throughout, and he tired easily during sustained efforts. Finger-to-nose movements were done smoothly. On sensory examination he had substantially diminished position sense in the toes bilaterally. Reflex examination revealed normal responses at the biceps, trace reflexes at the triceps and lower extremities, and no left patellar reflex. Plantar stimulation produced toe flexion bilaterally. Stance and gait were not tested.

Laboratory studies revealed normal complete blood count and blood chemistry levels. Serologic tests were negative for syphilis and the human immunodeficiency virus. The patient's angiotensin-converting enzyme level was normal. A purified protein derivative (PPD) test for tuberculosis was negative. A chest x-ray film and MRI scan were normal. Lumbar puncture results included a protein concentration of 3.4 grams per liter (340 mg per dl), a glucose level of 2.7 mmol per liter (49 mg per dl), and 0.17 monocytes (Table 1), with unremarkable cytologic findings. Cultures were nega-

*Assistant Clinical Professor, Department of Neurology, Reed Neurological Research Center, UCLA School of Medicine, Los Angeles, California.

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From the Department of Neurology, Reed Neurological Research Center; Department of Radiological Sciences; and Departments of Pathology and Neurology, Harbor-UCLA Medical Center, University of California, Los Angeles, School of Medicine.

Reprint requests to John C. Mazziotta, MD, PhD, Department of Neurology, Reed Neurological Research Center, UCLA School of Medicine, Los Angeles, CA 90024-1769.

ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomographic
ELISA = enzyme-linked immunosorbent assay
Ig = immunoglobulin
MRI = magnetic resonance imaging
PPD = purified protein derivative
SLE = systemic lupus erythematosus

tive for bacteria and fungi. Complement fixation was negative for coccidioidin in the CSF.

The patient was treated with a course of steroids and showed mild improvement in mental function. After appropriate cultures were obtained, he was started on a regimen of amphotericin B, isoniazid, and ethambutol hydrochloride, which was later changed to rifampin. The patient remained afebrile throughout his hospital course. A gastrostomy was done. Three weeks after admission, another lumbar puncture showed a protein concentration of 1.08 grams per liter (108 mg per dl), glucose 2.3 mmol per liter (42 mg per dl), 0.40 monocytes, and 0.05 neutrophils (Table 1). The patient became increasingly lethargic, aspiration pneumonia developed, and he died on July 9, 1989.

Neurologic Diagnosis

JOHN C. MAZZIOTTA, MD, PhD*: I will begin by describing the logic process required to arrive at a proper neurologic diagnosis. First, an anatomic localization must be determined in which the smallest volume of tissue in the nervous system is identified that explains all the signs and symptoms manifested by the patient. Next, a temporal profile of those signs and symptoms must be constructed, combined with the anatomic localization to produce the clinical localization. Add to that the laboratory data, of which only the spinal fluid is relevant in this case, to produce a combined clinical-laboratory localization, from which a differential diagnosis can be devised that is based on specific causes.

Let us begin by examining the patient's neurologic signs and symptoms in the temporal sequence in which they occurred. The time frame is referenced backwards from the time of death. Six months before death the first symptom, diplopia, was reported and identified as a left sixth nerve lesion. This finding contributes little to localizing the problem, and little progress would be made by examining the long list of causes for this phenomenon (Table 2).[1(p253)]

A month later, left facial weakness occurred. From the description, it is clear that this weakness resulted from a lesion at or beyond the nucleus of the left seventh nerve because the frontalis muscle was involved, as was the orbicularis oculi. Thus, with weakness of both the sixth and seventh nerves on the left, the site of abnormality is localized to the left pons at the middle to lower pontine level or along the course of the nerves emanating from that site.

At this point, it is not possible to identify whether the lesion involves intrinsic brain-stem structures or is extra-axial. Associated with the patient's facial weakness was the triad of hoarseness, nasal voice, and difficulty swallowing. This triad is seen with unilateral tenth nerve lesions. Bilateral tenth nerve lesions lead to cardiac rhythm disturbances, inability to swallow, and respiratory compromise, resulting in death. No specific information implicates the ninth nerve; taste was not tested on the posterior part of the tongue.

The patient also had problems with balance and tandem gait. Without testing Romberg's sign, the complaints imply either a cerebellar disorder or a sensory problem involving the peripheral nerves of the legs or the posterior columns of the spinal cord.

At the time of admission, numerous events occurred providing relevant information about neuroanatomic localization. First, the patient had a major motor seizure, denoting abnormalities of the cerebral cortex. Although nonlocalizing within the cortex, the fact that this seizure was generalized rather than focal indicates some irritation of the cerebral cortex, adding a new site in the nervous system for localization. The patient was also lethargic, slow, and confused about certain types of data but not others. His memory was good, he could define "junk bond," and his mental state improved after treatment with steroids and the placement of a ventricular catheter. While nonlocalizing, these new problems were indicative of bihemispheric dysfunction, perhaps associated with elevated intracranial pressure.

The patient also had a stiff neck. This adds another site of involvement, the meninges. Weakness of neck flexors is noted, implying bilateral 11th nerve dysfunction leading to weakness of the sternocleidomastoid muscles, or bilateral dysfunction of the upper cervical roots supplying other neck flexors, including the scalenes, or both.

The patient had mild papilledema, probably indicative of increased intracranial pressure. This is confirmed by the elevated CSF pressure on lumbar puncture at that time. Visual acuity was decreased in the left eye, indicating a retinal or optic nerve lesion on the left. There was internal and external ophthalmoplegia of the left eye. That is, the left pupil did not react to light either directly or consensually and there was no eye movement. This would indicate left-sided third, fourth,

*Professor, Departments of Neurology and Radiological Sciences, Reed Neurological Research Center, UCLA School of Medicine, Los Angeles, California.

TABLE 1.—*Cerebrospinal Fluid Results*

Laboratory Study	*Time Before Death*			
	6 Months	*5 Months*	*1 Month*	*~ 1 Week*
Protein, grams/liter	"Slightly increased"	4.23	3.40	1.08
Glucose, mmol/liter	?	1.7	2.7	2.3
Cell count*	0	0.19: 0.18 monocytes, 0.01 neutrophils	0.17 monocytes	0.40 monocytes, 0.05 neutrophils
Other negative results	VDRL, cryptococcal antigen, bacterial and AFB cultures	Cytology, bacterial and AFB cultures	Cytology, bacterial and AFB cultures, coccidioidin complement fixation	

AFB = acid-fast bacilli

*Values are expressed as a fraction of 1.

and sixth nerve lesions. On the right the situation was more complicated. The eye was not able to adduct or elevate, indicating third nerve dysfunction. There was incomplete abduction, however, indicating a partial problem with the right sixth nerve.

Next comes the question of the right fourth nerve. In a patient with a third nerve lesion who is able to depress the eye, this function occurs through the action of the superior oblique muscle by the fourth nerve. Depression of the eye with the fourth nerve also results in intorsion of the eye because the point of insertion of the superior oblique muscle results in rotation of the globe in addition to depression. No data about intorsion were provided on physical examination; thus, the right fourth nerve is assumed to have been functioning normally in this patient. These are the only new findings regarding the patient's right side.

An absent corneal reflex on the left provides further evidence of peripheral facial nerve involvement. Decreased hearing on the left implies an eighth nerve lesion, while decreased palate rise on the left again implicates the tenth nerve on that side.

Two additional findings identify a disorder outside of the cranial cavity. These include the decreased position sense in the toes, implicating a peripheral sensory neuropathy involving the lower extremities or problems with the posterior columns of the spinal cord. Because no other evidence of spinal cord dysfunction was recorded, the sensory finding is more likely to have resulted from peripheral nerve injury. An absent left patellar reflex can be attributed to a selective left femoral nerve mononeuropathy or a lesion of the midlumbar roots on the left.

Thus, we have a long, complicated list of problems; the goal is to combine them in a logical way. The lack of two findings in the history is notable. First, there were no clear cerebellar findings. Second, and more important, there were no long tract signs. The patient had normal tone, no pathologic reflexes, and, thus, no clear evidence of parenchymal brain disease. All the patient's findings can be explained by lesions external to the central nervous system. With intrinsic brain-stem lesions, long tract signs occur early. With extra-axial lesions surrounding the brain stem, long tract signs occur late, if at all, and this patient had none, indicating only extra-axial involvement.

What is the smallest site that explains most of the findings? The distribution of cranial nerve lesions can all be localized to the basal cisterns, concentrated on the left more than the right. This represents a small volume but can explain the entire constellation of signs and symptoms, except for the loss of position sense in the feet and the absent left patellar reflex. The neuroanatomic localization, therefore, is as follows: the basal cisterns, more on the left than the right, from the interpeduncular fossa to the medulla, in a contiguous fashion, with involvement of the left optic nerve and the cortex as indicated by seizure and lethargy; peripherally, left femoral nerve or midlumbar roots and either the distal sensory nerves to the feet, their roots, or the posterior columns of the spinal cord.

The temporal course of symptom progression in this patient indicates that the cranial nerve problems were additive. The symptoms are relentlessly progressive without remissions or change in quality, with the addition of more nerves in a contiguous fashion over the course of months. Thus, the temporal profile is subacute, progressive, and nonremitting, despite attempted therapies. The patient's mental state was normal until late in the course, then declined, responded to treatment with steroids, and declined again.

Now let us examine the systemic features of the disease. Abnormal findings were the provocative story of the tick bite and rash, which will be discussed later, a smoking history, and profound weight loss. The patient reported no fever, no history of travel, no drug use, only moderate alcohol consumption, no cranial or radicular pain, no history of problems with other organ systems, and no known risk factors for the acquired immunodeficiency syndrome.

The only systemic physical finding is that of cachexia. Presumably absent are skin lesions or findings that may represent other organ involvement or embolic phenomena. Combining these data with the neuroanatomic information and the temporal course, the description of this patient's disease is that of subacute, progressive spinal and cranial mononeuritis multiplex with cachexia and lack of fever.

TABLE 2.—*Causes of 6th Nerve Palsies**

Nonlocalizing
Increased intracranial pressure
Head trauma
Lumbar puncture or spinal anesthesia
Vascular hypertension
Diabetes mellitus
Parainfectious disease (postviral, middle ear infections in children)
Basal meningitis
Localizing
Pontine syndromes (infarction, demyelination, tumor)
Cerebellopontine angle lesions (acoustic neuroma, meningioma)
Clival lesions (nasopharyngeal carcinoma, clivus chordoma)
Middle fossa disorders (tumor, inflammation of medial aspect of petrous)
Cavernous sinus or superior orbital fissure (tumor, inflammation, aneurysm)
Carotid-cavernous or dural arteriovenous fistula

*From Glaser.[1]

Differential Diagnosis

For the description of this patient's disorder to be as complete as possible, before we compile a list of possible causes, it is appropriate to examine the laboratory data. The blood chemistry levels were normal, but the spinal fluid findings were revealing. Table 1 summarizes the four spinal fluid results. There was an increase in protein to rather high levels, and then a decline before death. The glucose level was low or borderline low, particularly in the second and third examinations. The cell count was elevated with a monocytic pleocytosis in the range of 0.20 to 0.45. Other study findings were consistently normal. These results represent a monocytic aseptic meningitis with borderline low glucose levels. Tuberculosis, cryptococcosis, coccidioidomycosis, syphilis, sarcoidosis, systemic lupus erythematosus (SLE), and carcinomatous meningitis all produce monocytic pleocytosis with elevated protein levels, borderline low glucose concentrations, and a range of cells similar to that seen in this patient. Thus, the CSF formulas provide guidance but are not specific.[2] Causes of aseptic meningitis without fever include all the disorders listed above. Thus, there are five diseases worthy of discussion in this patient: SLE, sarcoidosis, fungal meningitis, Lyme disease, tuberculosis, and carcinomatous meningitis.

Typical SLE patients are young women. They tend to have multiple systemic findings; this patient had only an

evanescent rash. There was no elevation of his sedimentation rate or an abnormal antinuclear antibody level. Nervous system disease in patients with SLE typically begins centrally with seizures, mental state changes, or behavioral alterations. These findings appear more prominently and earlier in the course with SLE than do peripheral nerve lesions—the reverse sequence of that seen in this patient. The CSF typically has a lower protein level than this patient had, and the glucose concentration is usually normal. Thus, this patient probably did not have SLE.

Sarcoidosis, for which this patient was tested, also has multiple systemic features, none of which were present. The chest roentgenogram and chest CT scan showed no adenopathy in the mediastinum; there were no ocular findings and no reports of changes in the calcium level. An angiotensin-converting enzyme level was normal in the patient, but it can be normal in 40% of patients ultimately diagnosed as having sarcoidosis. A substantial proportion (5% to 25%) of patients with sarcoidosis have neurologic symptoms. Central problems usually occur early in sarcoidosis, as in SLE, and are more prominent than later-appearing peripheral nervous system abnormalities; again, the reverse of this sequence occurred in our patient. Meningeal involvement with sarcoid would account for this patient's problems, with meningitis, typically subclinical, and monocytic pleocytosis with elevated protein and borderline to low glucose levels. There are often granulomas at the base of the brain in the areas that involve the second and seventh cranial nerves, but typical involvement may also include the hypothalamus and the pituitary. Most notable is the pace of the disease, which in typical neurosarcoidosis is slow, with two to three years elapsing before it is diagnosed. Our patient's disease progressed rapidly, with multiple neurologic problems and no systemic features, leading to death in six months. This patient did not have sarcoidosis.

Fungal meningitis is a possibility—in fact, one for which this patient was treated. Various fungal infections produce the symptoms and signs of aseptic meningitis with cranial neuropathies.[2,3] One group includes histoplasmosis, blastomycosis, candidiasis, and aspergillosis. These infections typically occur in immunocompromised patients, which was not the situation here. Meningitis is rarely found without systemic dissemination of the disease. Mucormycosis similarly occurs either with disseminated disease or, more typically, with obvious infection of the sinuses, nose, and orbit, none of which were present in this patient. The two most likely fungal infections—both of which the patient was tested and treated for—are coccidioidomyosis and cryptococcosis. The former is more frequent in nonwhites and immunosuppressed patients; this patient was neither. These patients typically have pulmonary findings and fever, which our patient did not have. As with the other fungal infections, brain involvement is rare without disseminated disease. The CSF was negative for coccidioidomycosis complement fixation.

Cryptococcosis, the most likely fungal infection in this patient, is found in patients with diabetes mellitus, steroid use, malignancy, or some other immunocompromising events.[3-6] Fever and pulmonary involvement are typical. Spinal fluid india ink preparations are positive in about half the patients, and CSF serologic test is positive for cryptococcal antigen in 85%, increasing to 94% if both blood and spinal fluid are examined. Frequently cryptococcosis causes the triad of problems this patient manifested: hydrocephalus, papilledema, and cranial nerve lesions. Because the systemic and historical features are lacking, however, I doubt this patient had cryptococcal meningitis.

Three final possibilities remain: Lyme disease, tuberculous meningitis, and carcinomatous meningitis. Lyme disease is implicated by the history of tick bite and rash.[7,8] Tick bite is the inciting event in Lyme disease, typically occurring one to two weeks before other symptoms start, and most patients do not recall the bite (this patient did) because the tick is so small. Ticks are 1 to 3 mm in length. The bites typically occur in the summer or fall, especially June and July. This patient would have been bitten in January, an unlikely time of year.

The illness has three phases. The first phase includes the rash, usually accompanied by a headache, and occurs within the first week. The second phase, occurring weeks to months later, includes cardiac problems (conduction defects), musculoskeletal problems (myalgias), arthritis, and neurologic problems (such as meningitis). Late disease, occurring months to years later, includes arthritis and demyelination of the central nervous system.

Lyme disease is a typical spirochetal infection, having all the systemic features seen with the clinical phases of syphilis or leptospiral infections. Neurologic symptoms are prominent.[7,9-13] Meningitis occurs a few weeks after the rash with headache and stiff neck, a CSF formula not too different from what we see in this patient, cranial nerve defects in a considerable number of persons (50% of them having facial nerve involvement, a third of those involved bilaterally), peripheral neuropathy, and encephalitis.[14,15] Laboratory findings include an elevated sedimentation rate and a negative VDRL. This patient also had indirect immunofluorescence and an ELISA assay. Typically there is a fourfold rise in titers between the time of the bite and the neurologic symptoms, but there were no abnormalities in this patient. About 5% of patients with Lyme disease are seronegative with full testing.[16-19] This patient had negative results on indirect immunofluorescence and both IgM and IgG ELISA testing.

The treatment of Lyme disease is effective in all stages and is identical to that used for syphilis, namely, penicillin or third-generation cephalosporins. This patient was treated for Lyme disease, had negative serologic tests, and did not recover—in fact, his condition deteriorated. I doubt he had Lyme disease.

Tuberculosis is a likely possibility in this patient.[6,20-22] Fewer than 20% of patients with nervous system involvement from tuberculosis have fever, and, when it occurs, it is typically low grade, often only detected when a patient is admitted to a hospital. Most patients with tuberculosis of the central nervous system have no history of pulmonary lesions; about half have normal chest films. An insidious presentation is possible, then, with the neurologic symptoms being the first abnormalities detected by the patient or physician. Sedimentation rate and PPD testing results can be normal. Meningitis typically begins with headache, lethargy, confusion, and stiff neck. Some of these features were present in our patient, but only after four or five months of illness. Cranial nerve defects are common, and oculomotor nerves are typically involved, a feature seen in this patient. This patient had increased intracranial pressure but no obvious obstruction of the ventricular system. In tuberculous meningitis, the patient not infrequently has aqueductal or

fourth ventricular obstruction. Brain infarction can occur, although none occurred in this patient. Contrast enhancement on CT scan typically occurs in the basal cisterns, particularly in patients with cranial nerve lesions. This patient had normal imaging studies.

The spinal fluid in tuberculous meningitis has cell counts that are higher than those seen in this patient. The CSF protein level tends to be elevated, although not as high as in this patient. The CSF glucose concentration is borderline low, and in some patients low. Smears are negative for acid-fast bacilli in most patients, and cultures can, at times, be negative even when obtained in triplicate. Tuberculosis is a tempting diagnosis, but there are enough subtle differences about this patient's course to exclude it. Most notable is the fact that he was treated for tuberculous meningitis, although late in his course, without response.

Carcinomatous meningitis can occur with almost every type of tumor, but most often with lung or breast cancer and melanoma.[23-27] Meningeal involvement as the only finding is unusual, occurring in not more than 5% of patients. Tumors can gain access to the subarachnoid space along nerves, through foramina, or in the blood. Cranial nerve involvement is seen in 80% of patients and can include the optic nerve. About 40% of patients have abnormalities on imaging studies,[28] such as increased ventricular size, which this patient had, and cisternal obliteration, which this patient did not. The typical CSF formula has an elevated protein level and, if there is diffuse disease throughout the subarachnoid space, a low glucose level. False-negative cytologic tests are common, with 45% typically negative on the first lumbar puncture, depending on the CSF volume.[29] Of major importance is the survival: These patients usually live two to six months after symptoms start and die of their tumor. This was the course followed by the patient. His condition deteriorated steadily once his physical problems began, and, ultimately, he died despite therapy for infectious agents.

I think this patient had carcinomatous meningitis. There is some question, however, about the source of the tumor. From the protocol, there is no evidence of involvement of the other organ systems known to produce carcinomatous meningitis. The chest radiograph and chest and abdominal CT scans were all normal. No evidence of pancreatic disease or lymphadenopathy in the neck, mediastinum, or abdomen was found. The patient's history of smoking is probably the only clue to the site. The most common tumor to present in the central nervous system without known primary or other metastatic sites is carcinoma of the lung, usually small-cell carcinoma.[23]

My conclusion in this case is that this patient had cancer and that his neurologic signs and symptoms were caused by carcinomatous meningitis, possibly of pulmonary origin, with involvement of the subarachnoid space diffusely (due to the low glucose level) and including the left optic nerve and perhaps even the optic disk. The tumor should have been found in the basal cisterns, more on the left than on the right, extending from the midbrain to the medulla. The lumbar roots should be involved on the left side as well, from L-2 to L-4. In addition, the patient had a sensory distal polyneuropathy due to carcinoma. He was cachectic because of carcinoma and also because of dysphagia caused by the cranial nerve dysfunction. The patient was evaluated carefully, but interventions for all conceivable, treatable causes of his disease were unsuccessful.

ANDREW CHARLES, MD*: When the residents were polled, nine voted for carcinomatous meningitis, five for granulomatous or tuberculous meningitis, and one for Wegener's granulomatosis. An inflammatory meningeal process was the unifying diagnosis thought to explain all the major findings. In addition, the patient had diffuse, generalized weakness exaggerated by sustained effort. This could be a manifestation of a paraneoplastic disorder. The Eaton-Lambert syndrome and peripheral neuropathy are two well-known paraneoplastic syndromes.

Pathologic Findings

HIDEO ITABASHI, MD†: The general autopsy was done by Willard F. Worthen, MD, of Daniel Freeman Memorial Hospital (Los Angeles, California). The body was that of an extremely cachectic man commensurate with the history of a 40-lb weight loss. The left eye was protected by an occlusive dressing. A gastrostomy tube was in place in the anterior upper abdominal quadrant. The lungs were congested but soft with dependent rubor. The pleural cavities contained approximately 150 ml of serosanguinous fluid on each side. The bronchi contained a large amount of mucus at the carina extending into both main-stem bronchi. No neoplasms or granulomas were found. The heart weighed 420 grams, and the coronary arteries showed moderate atherosclerotic disease without old or recent myocardial infarction. The gastrostomy stoma was secure, and the remainder of the general autopsy findings were unremarkable. The brain was sent to Harbor-UCLA Medical Center for examination.

The brain weighed 1,620 grams after fixation and was generally and greatly swollen with near-smooth flattening of all the convolutional surfaces. Leptomeninges over cerebral hemispheric convexities were thin and transparent, and superficial blood vessels were moderately and generally congested. At the base, cortical surfaces were flattened but devoid of herniation marks. Leptomeninges of the basal cisterns showed a faint clouding along the brain-stem base, particularly over the prepontine cistern (Figure 1). Special attention to the leptomeninges of the cerebellopontine angle regions showed no gross change. Optic, oculomotor, trigeminal, abducens, and left facial nerves were normal appearing (Figure 1). Both facial and acoustic-vestibular nerves were identified on the right, and both appeared swollen and boggy (Figure 1). The cerebellum was generally swollen, and the cisterna magna was filled with soft cerebellar fragments.

Coronal sections of the cerebral hemispheres revealed soft, swollen, and congested tissues with blurring of the gray-white junctions, characteristic of a "respirator" brain. Despite the swelling, the lateral ventricles were symmetric and normally patent, suggesting some degree of prior enlargement; there was no evidence of chronic expansion of the lateral angles, however. Otherwise, no gross abnormality was detected in the cerebrum. Multiple sections of brain stem and cerebellum revealed no abnormality other than slight thickening around the lower cranial nerve rootlet origins, and those were attributable to the "respirator" brain state (Figure 2).

Paraffin-embedded sections for a general survey of the brain were stained with hematoxylin and eosin. Selected sec-

*Resident, Department of Neurology, Reed Neurological Research Center, UCLA School of Medicine, Los Angeles, California.

†Professor in Residence, Departments of Pathology and Neurology, Harbor-UCLA Medical Center, Los Angeles, California.

tions were also stained with luxol fast blue-eresyl violet, Masson trichrome, periodic acid-Schiff, mucicarmine, and immunoperoxidase methods for glial fibrillary acidic protein and S-100 methods.

Distributed throughout the subarachnoid spaces at all levels of the brain, from the cerebral hemispheric vertex to the inferior cerebellar hemisphere (concentrated around the pons and medulla), there was leptomeningeal carcinomatosis composed of a well-differentiated, mucin-producing adenocarcinoma. Over the cerebral hemispheric convexities, the implants were microscopic, ranging from clusters of several hyperchromatic atypical cells to small rosettes of glandular formation (Figure 3). No intraparenchymal implant was present except for a single, minute, superficial focus along the Virchow-Robin space of the bases pontis. Glomera of the choroid plexuses of the lateral ventricles showed symmetric,

Figure 1.—The base of the brain shows semitranslucent leptomeningeal thickening overlying the interpeduncular and prepontine cisterns. **Double arrows** show boggy 7th and 8th cranial nerves on the right; **single arrow** points to the left 7th nerve, and **arrowhead** points to the left optic nerve surrounded by tumor.

Figure 2.—A transverse section of caudal pons is shown at the level of the facial colliculi. **Arrow** points to the root of facial nerve surrounded by tumor.

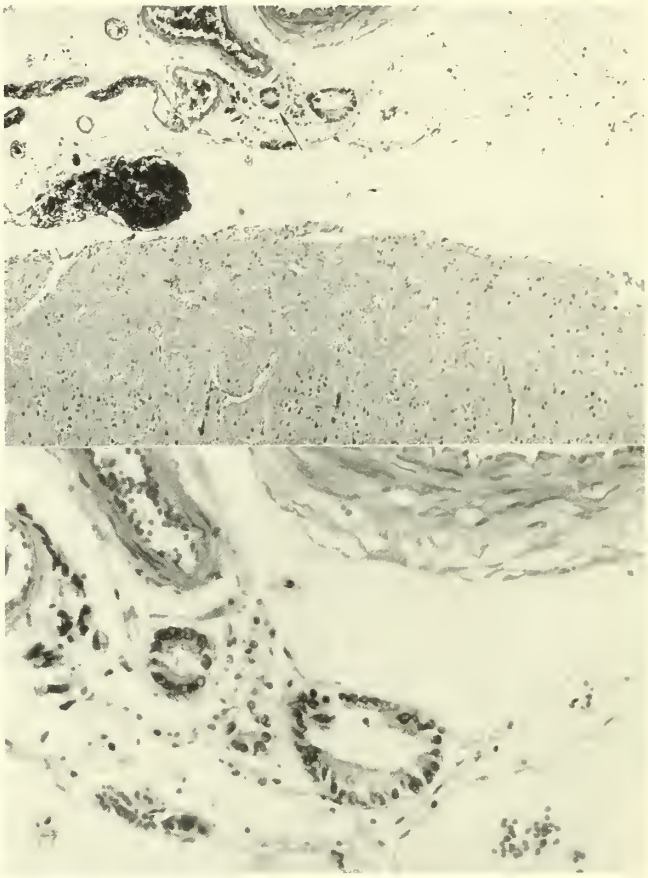

Figure 3.—**Top,** Shown at low power is a section of subarachnoid space over the cerebral hemispheric convexity that contains two small tumor implants **(arrow)** (hematoxylin and eosin stain, × 70 original magnification). **Bottom,** The tumor cells are shown at higher power (hematoxylin and eosin stain, × 250 original magnification).

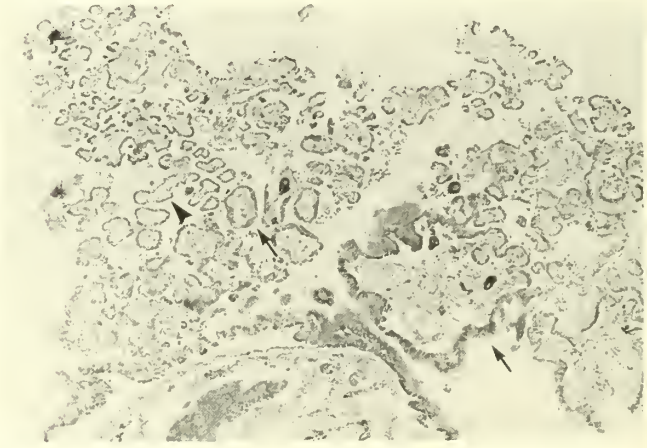

Figure 4.—Shown at low power is a portion of glomus of the choroid plexus showing residual choroid plexus at one end **(arrowhead). (Arrows)** Adenocarcinoma replaces choroidal epithelium (mucicarmine stain, × 30 original magnification).

near-total replacement by adenocarcinoma without enlargement. Only small sections of preserved fronds marked the site as choroid plexus (Figure 4). The choroid plexuses of the temporal horns were not involved, although tumor was present in the choroidal fissure against the opposing surface of the tela choroidea (Figure 5).

Other than changes associated with "respirator" brain, the cerebrum was free of abnormality, except for a single small focus of subacute infarction in the corpus callosum around dispersed tumor cells. No other abnormality was noted, except for a minute tumor implant in the supracallosal cistern forming an arc around an otherwise intact pericallosal artery.

The largest tumor aggregates were found around the brain stem, with the greatest collection on the dorsal and lateral aspects of the pons and medulla. A heavy accumulation was present expanding the quadrigeminal plate cistern overlying the inferior colliculus. Although the pia was hypertrophied, at no point did tumor penetrate it; subpial glia were hyperplastic, however. The tumor consisted of single-layered cords of cells usually forming small to large glandular rings composed of well-differentiated cells possessing peripherally displaced nuclei and pale foamy cytoplasm (Figure 6). Glandular spaces were filled with pale mucinous material, and mucin-positive substance stained the luminal side of the encircling cells. The luminal margins of the cells were fuzzy, suggesting a brush border.

At the cerebellopontine angle, the facial nerve on one side was degenerated and encased by tumor (Figure 7). An S-100 stain clearly showed small atrophic nerve bundles surrounded by tumor (Figure 8), and the ipsilateral facial nucleus showed neuronal dropout with some of the remaining

Figure 5.—Shown at medium power is a section of choroid plexus of the temporal horn lined by ependyma **(right). Arrows** point to adenocarcinoma in the depth of the choroidal fissure abutting on the tela choroidea (mucicarmine stain, × 42 original magnification).

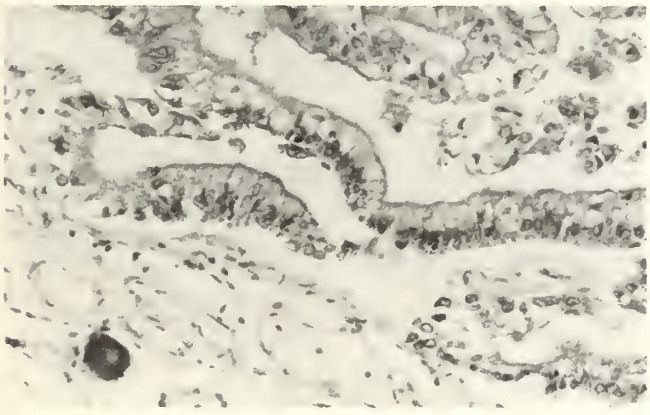

Figure 6.—A detail of well-differentiated adenocarcinoma shows nuclei along the abluminal side, pale cytoplasm, and a thin layer of mucicarmine-staining substance along the luminal surface (mucicarmine stain, × 250 original magnification).

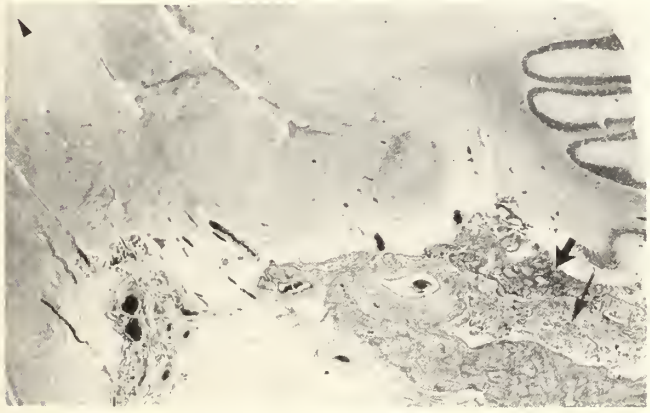

Figure 7.—Shown at low power is a section of cerebellopontine angle region showing a thickened cranial nerve rootlet expanded by infiltrative neoplasm. **Thin arrow** points to residual choroid plexus. **Large arrow** indicates adjacent tumor in the subarachnoid space. **Arrowhead** points to facial nucleus (luxol fast blue-cresyl violet stain, × 7.5 original magnification).

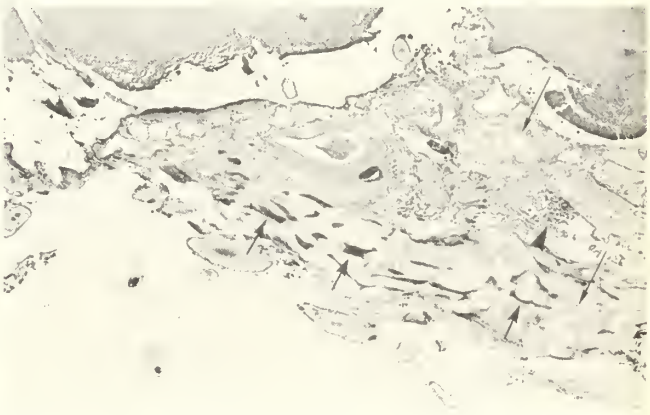

Figure 8.—A serial section to Figure 6 is stained with the immunoperoxidase method for S-100 protein. **Thin arrows** point to S-100-positive residual atrophic cranial nerve rootlets. Intervening relatively clear tissue is neoplastic **(small arrows),** and the arrowhead points to residual choroid plexus that is S-100 positive (× 9.5 original magnification).

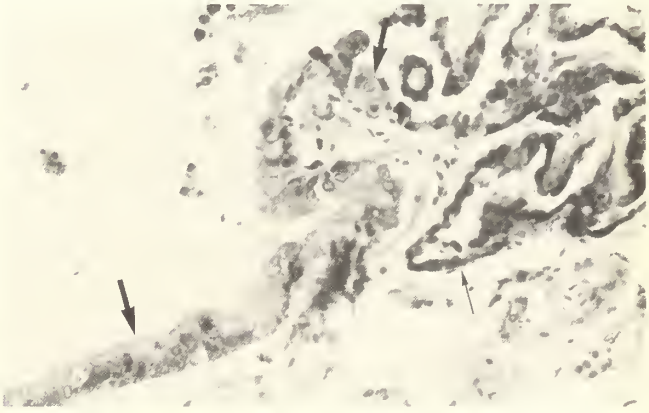

Figure 9.—Shown at high power is a detail of the transition zone between choroidal epithelium (small and dark staining indicated by **small arrow**) being replaced by adenocarcinoma **(large arrows)** (immunoperoxidase method for S-100 protein, × 160 original magnification).

cells showing axonal reaction. The intramedullary courses of the facial and acoustic nerves showed near-total loss of myelin and severe dropout of axons. On the same side, the choroid plexus of the lateral recess was replaced by adenocarcinoma similar to that seen in the glomus (Figure 9). Involvement similar to that of the facial nerve occurred around the optic chiasm and in the trigeminal root and the ninth and tenth cranial nerve rootlets.

The neuropathologic diagnosis was leptomeningeal carcinomatosis with well-differentiated adenocarcinoma and "respirator" brain.

Conclusion

Leptomeningeal carcinomatosis is a relatively uncommon form of metastatic disease of the central nervous system; about 300 cases have been reported in the literature.[30(p100)] Lung and breast have consistently led the list of primary sites, whereas the stomach, which was more commonly mentioned in the older literature, is now less frequently a primary site. The primary site of the adenocarcinoma in this case remained undetected; of 20 cases of Henson and Urich, 4 had unknown primary sites. In a Mayo Clinic series, five of seven cases of leptomeningeal carcinomatosis with lung primaries were adenocarcinomas[24]; a gastric primary cannot be ruled out in this case.

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Resolution of Pulmonary Edema
New Insights

Discussant
MICHAEL A. MATTHAY, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

FLOYD C. RECTOR, MD*: *The focus on pulmonary edema is usually on the mechanisms of formation. Little attention is paid to the other determinant of excess lung water, the clearance of edema fluid from the lung. The resolution of pulmonary edema will be discussed by Michael A. Matthay, MD, a member of the faculty of the Departments of Medicine and Anesthesia at UCSF and a member of the senior staff and of the Cardiovascular Research Institute, where his experimental and clinical research has included studies of the ion and protein transport properties of the alveolar epithelium.*

MICHAEL A. MATTHAY, MD†: The primary scientific objective of this work‡ has been to determine the mechanisms responsible for the clearance of liquid and protein from the air spaces of the lung. This scientific objective complements our clinical objective to develop a better understanding of the resolution phase of pulmonary edema.

By way of brief review, recall that physiologically there are two types of pulmonary edema: hydrostatic edema and increased permeability edema.[1-3] Hydrostatic pulmonary edema develops because of elevated pressure in the microcirculation of the lung, usually due to left-sided heart failure. About two thirds of clinical cases of pulmonary edema are related to elevated hydrostatic pressures in the pulmonary circulation. The other third of the cases are related to an increase in the permeability of the pulmonary capillaries from sepsis, gastric aspiration, and other causes of acute lung injury.

To appreciate the morphologic basis for the development of edema in the lung, it is necessary to recall the normal structure of the alveolar-capillary unit. The alveolar capillaries in the lung are surrounded by an interstitial space, which is separated from the air spaces by the alveolar epithelial barrier (Figure 1). Under normal conditions, some fluid and a small amount of protein filter into the interstitium from the alveolar capillaries through small gap junctions in the endothelium. The gap junctions between the cells of the normal alveolar epithelium are much tighter (Figure 1). This makes good sense teleologically because it is important that the air spaces remain dry for the lung to carry out its primary function of exchanging gas. Therefore, the alveolar epithelium should offer substantial resistance to the passive movement of liquid and protein into the alveoli.

In either type of pulmonary edema, an increased quantity of fluid moves from the vascular to the interstitial space of the lung. About 500 ml of edema fluid can collect in the interstitium of the lung before the interstitial pressure is high enough for edema fluid to break through the epithelium and flood the air spaces.[1,3]

Pulmonary edema fluid contains both liquid and protein. The initial specimen of pulmonary edema fluid from patients with cardiac failure has a protein concentration of about 30 grams per liter; in patients with increased permeability pulmonary edema, the protein concentration is usually higher, 40 to 60 grams per liter.[4,5] The distinction between hydrostatic and increased permeability pulmonary edema can usually be made by analyzing the ratio of the protein concentration in pulmonary edema to that in plasma.[4-6] If the ratio is 0.65 or lower, the edema fluid is a transudate, diagnostic of hydrostatic edema; if the ratio is 0.75 or higher, the fluid probably reflects increased permeability, although the edema fluid specimen must be obtained before resolution has begun (see later discussion of this issue). If the ratio is between 0.65 and 0.75, the type of pulmonary edema is indeterminate. The cellular content of the edema fluid depends on associated conditions, such as hemorrhage or inflammation. There are always some erythrocytes and a few monocytes in hydrostatic edema fluid; in most cases of increased permeability edema, the number of neutrophils is greater than in hydrostatic pulmonary edema.[7]

Resolution of Pulmonary Edema

Experimental Studies

To analyze the resolution phase of pulmonary edema, it is important to recognize that there are two extravascular

*Professor and Chair, Department of Medicine, University of California, San Francisco (UCSF), School of Medicine.

†Associate Professor, Departments of Medicine and Anesthesia, UCSF.

‡Other investigators in the Cardiovascular Research Institute, including Norman Staub, MD, Jonathan Widdicombe, DPhil, and Jeanine Wiener-Kronish, MD, made valuable contributions to the work presented here.

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Reprint requests to Homer A. Boushey, MD, Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT

PEEP = positive end-expiratory pressure
UCSF = University of California, San Francisco

spaces in which edema fluid can accumulate in the lung: the interstitium and the air spaces. When edema fluid is confined to the lung interstitium, the effects on gas exchange are usually minor. When it floods the air spaces, however, substantial gas-exchange abnormalities develop. For example, when the left atrial pressure is raised to a modest level—16 to 22 mm of mercury—only interstitial edema develops. The edema fluid collects in cuffs primarily around pulmonary arteries and airways (Figure 2).[8] As mentioned, the distensible interstitial space can absorb a considerable quantity of edema fluid before the interstitial edema moves into the air spaces. A chest radiograph shows increased interstitial markings such as Kerley's lines.[9,10]

Removing edema fluid from the lung interstitium is not a major problem. A number of radiographic studies have indicated that interstitial edema resolves within 12 to 24 hours.[9] The edema fluid can be removed through several pathways including the lung lymphatics and the pulmonary or bronchial circulation. Also, the pleural space has recently been shown to be an important pathway for clearing edema fluid from the lung. Wiener-Kronish and Broaddus and co-workers have shown in both experimental and clinical studies that as much as 25% of edema fluid will move from the lung into the pleural space in both hydrostatic and increased permeability edema.[11,12]

The development of alveolar edema results in much more extensive pulmonary edema, which can be appreciated radiographically.[13] Moreover, removing edema fluid from the air spaces of the lung presents a substantially different problem from clearing it from the interstitium. The major reason for this difference is the presence of the tight epithelial barrier, which normally has a low permeability to both macromolecules and solutes.[14-16] Thus, the removal of edema fluid from the alveoli of the lung first requires that the fluid move across the tight epithelial barrier before it reaches the lung interstitium where, as mentioned, there are several readily available clearance pathways.

In our initial studies, we developed an experimental model that reproduced some of the clinical features of pulmonary edema. Because edema fluid is composed of both a liquid and a protein fraction, we designed the experiments to study alveolar liquid and alveolar protein clearance simultaneously. Therefore, we instilled autologous serum (2 to 3 ml per kg of body weight) into the distal air spaces of one lung.[16,17] This was done with a bronchoscope in large animals (sheep or dogs) and with a catheter in small animals (rabbits and rats). In the larger animals, the instilled volume was about 100 ml of serum into one lower lobe. The serum was stained with Evans blue so that at the end of the experiment we could determine that it was localized to one lower lobe. We also added to the instilled serum ^{125}I-labeled albumin to provide a quantitative marker for the instilled alveo-

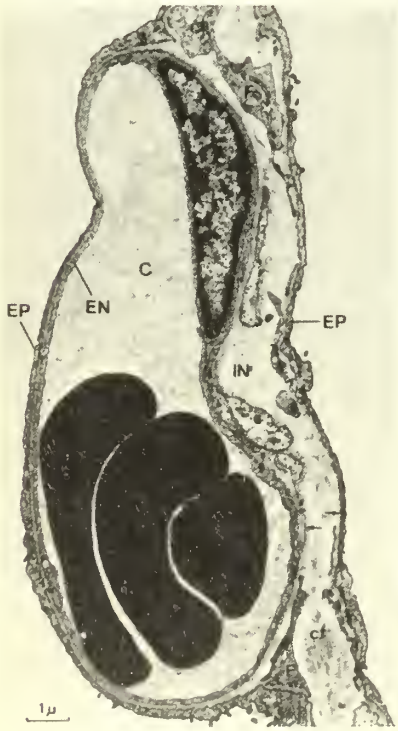

Figure 1.—Electron micrograph of a cross-section of an alveolar capillary (C) from human lung. Blood cells are suspended in the interalveolar septum between two alveolar spaces. The alveolar epithelium (EP) is the barrier that separates the air spaces from the interstitium (IN). Fluid and protein exchange probably occurs through small gaps between the endothelial cells (EN) in the alveolar capillaries. Connective tissue fibers are found in the interstitium, where the basal laminae (arrows) of the epithelium and endothelium are separated (reproduced with permission from Fishman et al[2(p4)]). cf = fibroblast cell

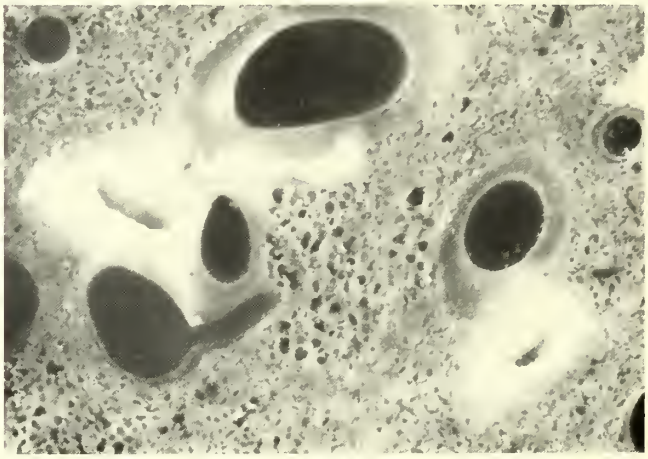

Figure 2.—The photograph shows a specimen of frozen sheep lung. In this experimental study, the left atrial pressure was elevated to 20 cm of water for 4 hours. The result is interstitial pulmonary edema with perivascular fluid cuffs around pulmonary arteries and small airways. There are some lymphatics visible in the fluid cuffs also (reproduced with permission from George[8(p442)]).

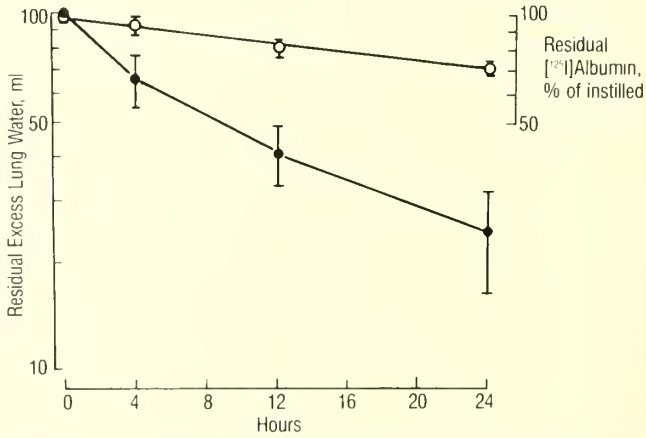

Figure 3.—The removal rate of 100 ml of excess water and ^{125}I-labeled albumin over 24 hours is plotted logarithmically. Solid circles represent the means ± the standard deviation (SD) of residual excess water left in serum-instilled lobe at 4, 12, and 24 hours. Open circles represent the means ± SD of residual [^{125}I]albumin in experimental lung expressed as a percent of the total instilled [^{125}I]albumin at 4, 12, and 24 hours (reproduced with permission from Matthay et al[17]).

lar protein that would enable us to determine how much of the protein tracer remained in the lung at the end of the study and how much entered the lung lymph and plasma during the study. The experiments lasted from 1 to 24 hours. At the end of each experiment, the lungs were removed and a catheter was wedged through the airways into the distal air spaces of the serum-instilled lung to obtain a specimen of the residual alveolar fluid. The total protein concentration, the radioactivity, and the cell count of that specimen were measured. Biopsy specimens were taken for histologic study, and the lungs were then homogenized separately; the excess liquid volume remaining in the serum-instilled lung was determined gravimetrically.

Our early studies in sheep showed that excess liquid is cleared from the air spaces at a much faster rate than is protein.[16,17] About 75% of the liquid volume but only 25% of the protein was removed from the lung by 24 hours (Figure 3).[17] The differential clearance rates for liquid and protein were related to the slower clearance of protein across the tight alveolar epithelial barrier. In fact, we found that the protein concentration of the serum that was instilled into the air spaces of one lung progressively increased to levels well above the plasma protein concentration.[16]

A substantial rise in the alveolar protein concentration was evident after only four hours. In one series of experiments, we found that by four hours after the instillation of 100 ml of autologous serum into one lower lobe, a third of the liquid volume had been removed from the lung and the protein concentration increased from 63 to 84 grams per liter (Table 1). Thus, the alveolar protein concentration was about 20 grams per liter higher than the plasma protein concentration. This observation led us to propose the hypothesis that there must be an active ion transport system removing liquid from the air spaces.[16]

Further support for this hypothesis was obtained when the 4-hour studies were extended to 12 and 24 hours.[17] Over the longer time periods, there was a progressive clearance of the alveolar liquid so that the instilled protein in the serum in the air spaces increased to 129 grams per liter by 24 hours (Table 1). Thus, the protein osmotic pressure of the alveolar fluid was very high. This was further evidence that there must be an active ion transport mechanism involved in removing liquid from the air spaces of the lungs.

To examine our hypothesis, we tested various specific sodium and chloride channel inhibitors. We used furosemide, for example, which inhibits sodium chloride cotransport, but this agent had no effect at the alveolar epithelial level.[17] Using amiloride, however, had a substantial effect. Amiloride blocks the uptake of sodium across the apical epithelium. In our sheep studies, amiloride inhibited about 50% of the clearance.[18,19] Other investigators showed that type II alveolar epithelial cells formed fluid domes when they were cultured in monolayers. The formation of these domes could be inhibited by removing sodium from the medium or by administering amiloride.[20,21]

In the cell culture studies, some investigators found that if a β-adrenergic agonist was applied, dome formation was greater.[22] Therefore, we did a series of studies in sheep in which we added terbutaline (a β_2-adrenergic agonist) to the serum that was instilled into the air spaces.[23] The terbutaline increased alveolar and lung liquid clearance dramatically. This effect did not depend on terbutaline-induced changes in hemodynamics, blood flow, or lung lymph flow.[23] Also, amiloride blocked 90% of terbutaline's effect. Thus, we concluded that in sheep, β-agonists dramatically increased alveolar liquid clearance by augmenting sodium transport from the air spaces. Subsequently terbutaline was found to also increase alveolar liquid clearance in dogs.[24]

As mentioned, amiloride inhibited 50% of basal liquid clearance in sheep, and in subsequent studies, we found that this agent blocked 75% of basal liquid clearance in rabbits.[25] What about the remaining 25% to 50% of alveolar liquid clearance? Could it be that the remaining fraction of clearance depends on a hydrostatic pressure gradient generated by ventilation? In earlier studies, the rate of alveolar liquid clearance in sheep and dogs was found to be the same whether the sheep were ventilated with positive pressure or were breathing spontaneously.[16,17,24] We had not ruled out the possibility that passive transmission of the pressure across the epithelium might also contribute to alveolar liquid clearance.

To answer that question, we did an additional study in sheep. Serum (3 ml per kg) was instilled into the left lung and then the left bronchus clamped so that the lung would not be ventilated. The sheep was ventilated by the right lung only. Even in the absence of ventilation, alveolar and lung liquid clearance from the left lung over four hours was normal.[26] This finding provided additional evidence that all of alveolar epithelial solute and liquid clearance depends on an active ion transport process.

Overall, we have studied three species: dogs, sheep, and rabbits. All have a similar pattern of alveolar liquid clearance with an increase in alveolar protein concentration to levels well above the plasma protein concentration, but the rate of alveolar liquid clearance varies among species. Dogs have the slowest basal clearance, sheep have an intermediate rate, and rabbits have a fast rate of alveolar liquid clearance (Table 2). The mechanism for this species difference may be related to the number or the activity of the sodium transport channels in the epithelium.

TABLE 1.—*Alveolar Liquid Clearance in Sheep as Reflected by Progressive Concentration of Protein in the Air Spaces of the Lung**

Time, h	Alveolar Protein Concentration, grams/liter		Lung Liquid Clearance, % of Instilled§
	Initial†	Final‡	
4	63±6	84±6	33.2
12	59±4	102±12	59.2
24	64±6	129±19	75.9

*Data are shown as mean ± standard deviation.

†The initial alveolar protein refers to the protein concentration of the instilled serum (3 ml/kg).

‡The increase in concentration of protein in the air spaces can be used to estimate the alveolar liquid clearance by a simple proportion calculation because the instilled volume and the initial and final alveolar protein concentration are known (Berthiaume et al[23,24]).

§The clearance of liquid from the lung was calculated by the gravimetric method (Matthay et al[16,17]).

TABLE 2.—*Estimated Basal Rates of Alveolar Liquid Clearance in Dogs, Sheep, and Rabbits*

Species	Half-life for Alveolar Liquid Clearance, h	Source
Dogs	18	Berthiaume et al, 1988[24]
Sheep	9	Matthay et al, 1985[17]
Rabbits	6	Smedira et al, 1991[25]

Clinical Studies

In recent clinical studies, Wiener-Kronish and I have studied the resolution of pulmonary edema in humans.[27] The primary objective of these studies was to test the hypothesis that alveolar protein concentration would increase as alveolar edema was cleared from the air spaces of the lung. If we established that this was the pattern for the resolution of alveolar edema in humans, this information would provide further evidence for the hypothesis that active ion transport was important in humans as a critical mechanism for the clearance of excess alveolar fluid.

All patients who had sufficiently severe pulmonary edema to require mechanical ventilation were entered in the study. A specimen of pulmonary edema fluid was taken by suctioning through the endotracheal tube with a standard 14-gauge French catheter wedged into the distal bronchi within 15 minutes after endotracheal intubation. At the same time, a specimen of plasma was obtained for protein concentration, arterial blood gas measurements were done, and a chest radiograph was taken. A subsequent edema specimen was obtained if the patient's oxygenation improved as indicated by a decrease in the alveolar-arterial oxygen pressure difference by 50 mm of mercury; if the patient's oxygenation worsened as indicated by an increase in the alveolar-arterial oxygen pressure difference by 50 mm of mercury or more; or if there was a need to increase positive end-expiratory pressure (PEEP) by 3 cm of water or more to maintain oxygenation. If there was no change in oxygenation or the PEEP level, then a final edema fluid specimen was obtained at 12 hours.

A total of 34 patients were enrolled in the study.[27] Of these, 24 improved clinically as defined by better oxygenation and a decrease in edema on the chest film. Of these 24 patients, 15 had hydrostatic edema and 9 had increased permeability edema. Ten patients did not clinically improve. The initial alveolar-arterial oxygen pressure difference was similar in the two groups (Table 3). The final specimen in the patients with clinical improvement was obtained, as indicated, when the alveolar-arterial oxygen pressure difference had improved. The time interval for the final edema fluid specimen was similar in all patients. In contrast, of the ten patients with no improvement, seven had increased permeability and three had hydrostatic edema. Their initial alveolar-arterial oxygen differences were similar at the outset to those of the patients who improved (Table 3).

Chest radiographs correlated with the oxygenation data in 90% of the patients. Specifically, in 21 of the 24 patients whose oxygenation improved, the chest radiograph taken at the time of the second edema fluid specimen showed less pulmonary edema (Figure 4).

Of the 15 patients with hydrostatic pulmonary edema who improved clinically, the edema fluid protein concentration increased from the initial value in every patient, with no change in the plasma protein level (Table 4). The three patients with hydrostatic edema who did not improve had no change in their edema fluid protein concentration. Thus, the resolution of alveolar edema in hydrostatic alveolar edema was associated with an increase in the edema fluid protein concentration.

What happened to the nine patients with increased permeability who improved clinically? All of these patients had an increase in their edema fluid protein concentration to a mean level of 68 grams per liter (Table 4). In several of the patients, the final edema fluid protein concentration exceeded the plasma protein level. This result matched well with our experimental studies, which had shown that alveolar protein levels would rise well above the plasma protein level.[11,16,17,23,24] The seven patients with increased permeability edema who did not improve had no change in the alveolar edema protein concentration between the initial and follow-up specimens.[27]

TABLE 3.—*Alveolar-Arterial Oxygen Pressure Difference in Patients With Pulmonary Edema*†*

Classification of Edema	Patients, No.	Alveolar-Arterial Oxygen Difference, mm of mercury		Time Interval, h
		Initial	Final	
Clinical Improvement				
Hydrostatic	15	545±74	366±124‡	4.5±2.9
Increased permeability	9	553±40	368±112‡	6.8±5.1
No Clinical Improvement				
Hydrostatic	3	588±23	616±22	5.3±5.8
Increased permeability	7	518±84	538±95	5.4±4.1

*From Matthay and Wiener-Kronish.[27]
†Data are shown as the mean ± standard deviation.
‡$P<.01$ when comparing the final with the initial alveolar-arterial oxygen difference.

TABLE 4.—*Rates of Alveolar Fluid Clearance in Hydrostatic Versus Increased Permeability Pulmonary Edema in Patients With Clinical Improvement**

Classification of Edema	Patients, No.	Total Protein Concentration, grams/liter†		Concentration (%) Over Baseline§ Rate of Resolution, %/h	
		Initial	Final	Range	Mean†
Hydrostatic	15	33±10	48±23‡	3-39	12±10
Increased permeability	9	47±9	68±16‡	3-24	11±8

*From Matthay and Wiener-Kronish.[27]
†Data are shown as the mean ± standard deviation.
‡$P<.01$ compared with the initial edema fluid protein concentration.
§Concentration of the total protein in the final edema specimen compared with the initial edema specimen divided by the time interval in hours between the specimens provides an estimate of alveolar fluid clearance (Sprung et al,[6] Matthay et al[16,18]).

Thus, these results confirmed our basic hypothesis: as alveolar liquid was cleared from the air spaces, the edema fluid protein concentration would rise. As a specific example, consider the data on a patient who initially presented with a protein concentration in pulmonary edema fluid of 44 grams per liter and a plasma protein level of 70 grams per liter. He had hydrostatic edema (ratio, 0.64). The measured protein osmotic pressure on the initial pulmonary edema fluid was 20 mm of mercury. Four hours later, when the patient's oxygenation was improved and the chest radiograph showed less pulmonary edema, a follow-up edema fluid specimen had a protein concentration of 111 grams per liter, with a plasma protein of 70 grams per liter. The measured protein osmotic pressure of the edema fluid was 72 mm of mercury. Thus, these data showed that in humans, alveolar protein can concentrate to high levels and that there could be a large protein osmotic pressure gradient from the air spaces to the vascular bed.

This clinical study also gave us an opportunity to estimate the rate of alveolar liquid clearance in patients who had resolving hydrostatic or resolving permeability edema. We did not anticipate when we began the study that so many patients with increased permeability edema would have such rapid clearing. We thought that the resolution of pulmonary edema in humans would have to be studied primarily in patients with hydrostatic (cardiogenic) pulmonary edema because permeability edema would resolve too slowly for a short-term (12-hour) clinical study. But, as the data indicate, at least half the patients with increased permeability edema had their pulmonary edema resolve at a rate similar to that found in patients with hydrostatic edema (Table 4). Among those whose edema resolved, the mean rate of clearance was 12% per hour in the hydrostatic group versus 11% per hour in the increased permeability group.

We estimated the rate of alveolar liquid clearance from the measurement of changes in the protein concentration in edema fluid obtained from the air spaces in humans and compared these data with those in the other species we have studied (Table 2). From this estimate, it appears that humans have a rapid rate of alveolar liquid clearance. Alveolar liquid clearance in dogs, although slow, can be stimulated with β-agonist therapy; the intermediate rate of alveolar liquid clearance in sheep also increases with β-adrenergic agonist therapy. The basal clearance in rabbits does not respond to the use of terbutaline. We do not know whether alveolar fluid clearance in humans can be accelerated with β-adrenergic agonists.

Alveolar Epithelial Barrier

Prognostic Implications

As our clinical study progressed, it became clear that there were at least two populations of patients with increased permeability pulmonary edema, or the adult respiratory distress syndrome.[27] Group A included the nine patients who had an increase in edema fluid to plasma protein ratio of 10% or more in sequential specimens compared with the baseline value (Figure 5). Group B included the seven patients who had no change in their ratio of baseline edema fluid to plasma protein concentration throughout the course of the study, which indicated that the net quantity of edema in the air spaces was not decreasing (Figure 5).

In group A, mortality was only 22% (2 of 9). In fact, even the two patients who eventually died had recovered from their acute respiratory failure. One died of pulmonary embolism weeks later, and the other died of advanced carcinoma. Thus, all nine of these patients actually recovered from their acute respiratory failure and increased permeability pulmonary edema. In contrast, mortality was 71% in the group B patients (5 of 7). Of the two who lived, both required mechanical ventilation, one for 90 days and the other for 30 days. Although we studied only a small group, our findings suggest that determining the edema fluid protein concentra-

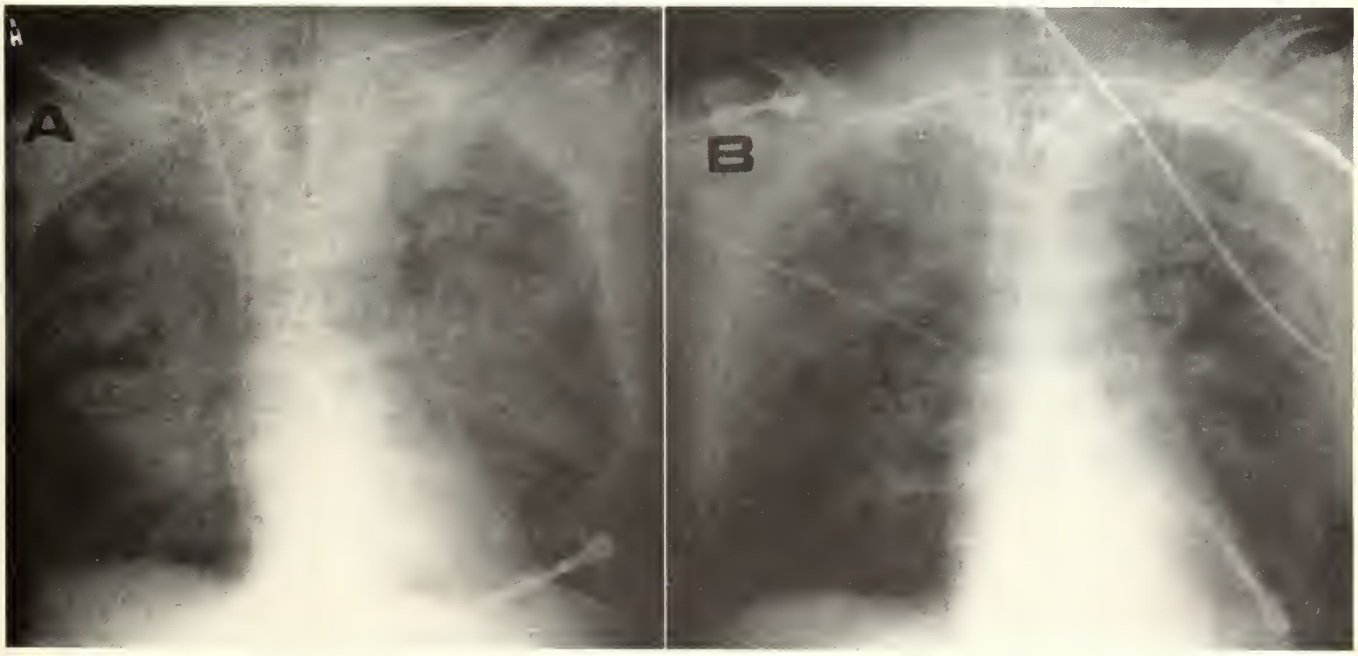

Figure 4.—A, Anteroposterior portable chest radiograph was taken of a patient following cardiopulmonary bypass in whom increased permeability pulmonary edema developed. The pulmonary arterial wedge pressure was 9 mm of mercury. The initial pulmonary edema fluid:plasma protein ratio was 0.85 at the time of this chest radiograph. **B,** Four hours later, a repeat chest radiograph was taken when the alveolar-arterial oxygen difference had decreased and a second pulmonary edema fluid: plasma protein concentration ratio had increased to 1.2. Note that the extent of pulmonary edema is significantly less on this second chest radiograph.

tion in the first 12 hours after acute lung injury might be useful as a prognostic indicator of the severity of acute lung injury.

Were there other factors that influenced this outcome? The pulmonary arterial wedge pressure did not differ between the two groups. Thus, the difference between the groups was not related to differences in cardiac function or intravascular pressures. Also, the initial PEEP levels were the same in the groups, although the final level of PEEP was higher in group B, reflecting the need for higher levels of PEEP to support oxygenation.

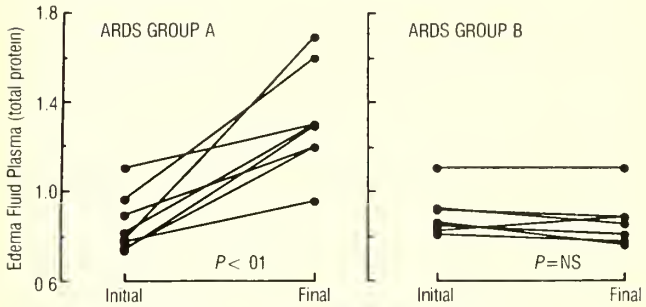

Figure 5.—Individual data points are shown for the initial and final pulmonary fluid-to-plasma total protein concentration ratio in 9 patients with the adult respiratory distress syndrome (ARDS) who clinically improved (group A) compared with the 7 ARDS patients who did not clinically improve (group B). The time interval between the initial and final specimen was similar between the group A (6.8 ± 5.1 hours) and the group B (5.4 ± 4.1 hours) patients (from Matthay and Wiener-Kronish,[27] reprinted with permission from the American Thoracic Society).

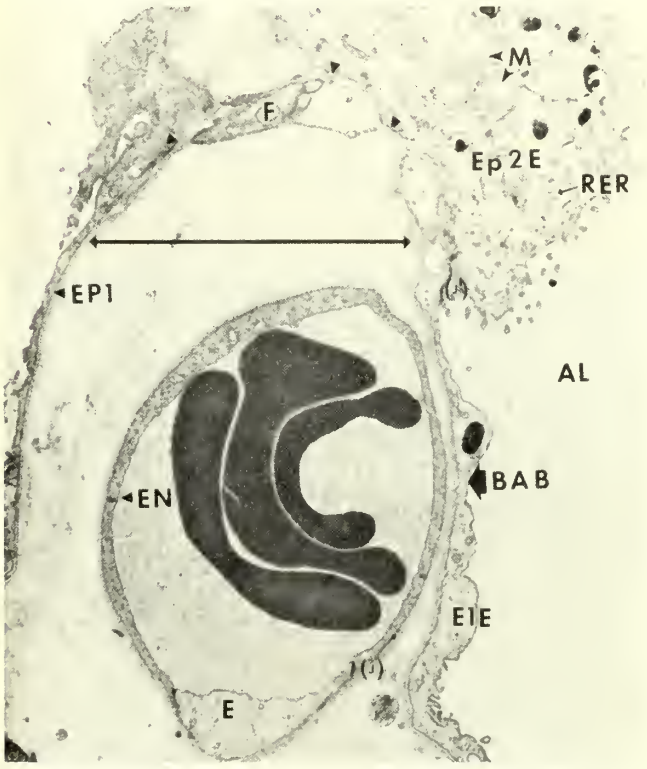

Figure 6.—Human interstitial edema with cellular injury is shown. The connective tissue space (long arrow) is markedly swollen, whereas the blood-air barrier (BAB) is normal. Normal gray capillary endothelial (EN) and type I epithelial cells (EP1) serve as built-in controls for swollen endothelial (E), type I epithelial (E1E), and type II epithelial (Ep2E) edematous cells. Epithelial type II cells also show degenerative features with swollen mitochondria (M) and degranulating rough endoplasmic reticulum (RER). Interstitial fibrocyte (F) anchors the epithelial basement membranes (arrow heads). J and J' are endothelial and epithelial junctions (from Fishman and Renkin,[2(p4)] reprinted with permission from the American Physiological Society). AL = alveolus

What was the distribution of clinical disorders associated with the adult respiratory distress syndrome in these groups? Sepsis was more frequently associated with acute lung injury in the group B patients. In group A, two patients had sepsis, two had a blood product reaction, two had complications after a cardiopulmonary bypass, one had gastric aspiration, and two had overdosed drugs. Sepsis has been reported to be a more lethal and severe form of acute lung injury.[28]

In summary, sequential specimens of pulmonary edema fluid in the first 12 hours after endotracheal intubation appear to identify two groups of patients with acute lung injury. In one group, alveolar epithelial barrier function appears to be relatively intact whereas in the other group lung injury appears to be more severe with damage to both the endothelium and epithelium. Mortality is apparently lower in the patients with intact alveolar epithelial barrier function. In fact, in the classic study by Bachofen and Weibel of patients who died of acute lung injury following sepsis, all patients had evidence of both lung endothelial and alveolar epithelial injury.[29] Other investigators have also reported alveolar epithelial injury in patients who have died in the acute phase of the adult respiratory distress syndrome (Figure 6).[30]

Conclusions

Both experimental and clinical studies support the conclusion that active ion (sodium) transport is the primary mechanism responsible for the clearance of excess liquid or edema fluid from the air spaces of the lung. Second, the integrity of the alveolar epithelium is an important factor in determining the extent of acute lung injury and survival in patients with acute lung injury. More experimental studies are needed to identify mechanisms that cause injury to the alveolar epithelium, a critical barrier in determining the extent of acute lung injury.

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Epitomes

Important Advances in Clinical Medicine

General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general and family practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in general and family practice that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

New Guidelines to Prevent Atherosclerosis

ATHEROSCLEROTIC DISEASE is responsible for about 700,000 deaths per year in the United States, with the majority resulting from ischemic heart disease. The National High Blood Pressure Education Program created in 1973 and the series of Surgeon General's reports on smoking issued since 1964 have raised public and professional awareness of the importance of these two particular risk factors. In a similar vein, the National Cholesterol Education Program (NCEP) was launched in 1987 with guidelines for the detection, evaluation, and treatment of hyperlipidemia. To cause a continued decline in cardiovascular mortality, the program recommends that all adults aged 20 years and older should have their total cholesterol levels measured at least once every five years. Although controversy exists about whether overall mortality is reduced by cholesterol reduction, there is a general consensus that control of this risk factor is beneficial.

Total cholesterol levels can be measured in a nonfasting person with further follow-up, including cholesterol fractionation, dependent on the total blood cholesterol level and the existence of other risk factors. Desirable blood cholesterol levels are less than 5.17 mmol per liter (200 mg per dl). Persons with cholesterol levels in the range of 5.17 to 6.18 mmol per liter (200 to 239 mg per dl) are designated as borderline high, and those with levels greater than 6.21 mmol per liter (240 mg per dl) are at high risk. Because of individual variation and laboratory inaccuracy, elevated cholesterol levels should be rechecked within eight weeks. If this level is within 0.78 mmol per liter (30 mg per dl) of the first, the average of the two levels should be used. If the second measurement is outside of this range, then a third test should be done. The average of these three becomes the patient's cholesterol level. Lipid measurements within three months of a major illness are not considered to be clinically relevant.

A careful history and physical can help detect secondary (and possibly reversible) causes of high-risk hyperlipidemias such as hypothyroidism, nephrotic syndrome, diabetes mellitus, obstructive liver disease, and cholesterol-elevating drugs, particularly progestins and anabolic steroids.

A person in the borderline-high group who has definite coronary artery disease or two risk factors, including male sex, family history of coronary artery disease, diabetes mellitus, obesity, cigarette smoking, hypertension, or a low high-density-lipoprotein (HDL) level—less than 0.91 mmol per liter (35 mg per dl)—should be considered at high risk, and decisions regarding treatment should be based on a fasting lipoprotein analysis that measures actual levels of low-density lipoproteins (LDLs) and HDL levels. Using these cutoff points, 25% of the adult population will have a cholesterol level in the high range (total cholesterol greater than 6.21 mmol per liter or LDL level greater than 4.13 mmol per liter [160 mg per dl]).

Dietary therapy using the American Heart Association (AHA) step I diet consists of 30% or less of calories from fat, including less than 10% of total calories from saturated fatty acids, and a cholesterol intake of less than 7.76 mmol per liter (300 mg per dl). If three months on this regimen does not lower cholesterol levels adequately, the AHA step II diet should be considered, which further reduces saturated fats to less than 7% of total calories and cholesterol to less than 200 mg per day. If these persons are unable to bring their level into a normal range despite six months of dietary therapy, then drug therapy should be considered.

With the aggressive reduction of cholesterol levels, there is a potential not only to halt atherosclerotic lesion formation but also to possibly regress the size of existing plaques.

STEPHEN BRUNTON, MD
Long Beach, California

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New Guidelines for Tuberculin Skin Test Interpretation

UNTIL 1983, the incidence of active tuberculosis in the United States had been decreasing steadily. Since then it has been increasing. Today a high incidence is reported among recent immigrants from the third world; other ethnic minority populations, especially African Americans, Hispanics, and Native Americans; those infected with the human im-

TABLE 1.—*Criteria for Determining the Need for Preventive Therapy*

Category	*Age < 35 Years*	*Age ≥ 35 Years*
No risk factor, low-incidence group	Treat if PPD ≥ 15 mm	Do not treat
No risk factor, high-incidence group†	Treat if PPD ≥ 10 mm	Do not treat
Risk factor* present, either incidence group	Treat all ages if PPD ≥ 5 mm and has HIV infection, recent contact with infectious person, or fibrotic lesions on chest radiograph	
	Treat all ages if PPD ≥ 10 mm and there is recent tuberculin skin test conversion (≥ 10 mm increase for those younger than 35; ≥ 15 mm increase for those 35 years and older); intravenous drug use; or patient has medical conditions that may increase risk of tuberculosis	

*Risk factors include HIV infection, recent contact with infectious person, fibrotic lesion on chest radiograph, recent tuberculin skin test conversion, intravenous drug use, or the presence of medical conditions that may increase the risk of tuberculosis, such as diabetes mellitus, silicosis, immunosuppression, or malnutrition.

†High-incidence group includes foreign-born persons from high-prevalence countries, African Americans, Hispanics, Native Americans, and residents of long-term-care facilities and correctional institutions.

munodeficiency virus (HIV); and elderly residents of long-term-care facilities.

The best way to identify persons infected with tubercle bacilli is the intradermal purified protein derivative (PPD) skin test. The tuberculin skin test is one of the oldest medical technologies still in daily use. Tuberculin was first derived by Koch in 1890; Mantoux, a French physician, developed the intradermal skin test in 1908; and purified protein derivative of tuberculin was first produced in 1934. Despite 50 years of research, there still is no better screening test for determining who has been infected and, therefore, who is at risk for active tuberculosis developing.

Unfortunately, the cross reactivity of the skin test with nontuberculous mycobacterial exposure frequently results in positive tests in those who come from areas of high nontuberculous mycobacterial prevalence—such as southern United States—or in those who have had a bacille Calmette Guérin (BCG) vaccination, which is still used in many Asian and Central and South American countries. The size of this reaction is usually from 10 to 15 mm of induration but may be boosted by repeated testing. On the other hand, using 10 mm as a cutoff point may give false-negative interpretations in situations where it is important to offer preventive therapy—such as those recently infected or who are HIV-positive.

These factors have prompted the Centers for Disease Control's (CDC's) Advisory Committee for the Elimination of Tuberculosis to change the criteria for recommending isoniazid preventive therapy. These new criteria, based on age, incidence, and risk factors, are given in Table 1.

The two key changes are the recommendation that a PPD result of 5 mm or more of induration is a positive test in populations with risk factors for *Mycobacterium tuberculosis* infection and that a PPD reaction must be 15 mm or more to be interpreted as positive in those at low risk. This latter change is to avoid false-positive interpretations and to minimize potentially inappropriate preventive therapy.

Regardless of the CDC's criteria changes, isoniazid preventive therapy (300 mg per day for 6 to 12 months) works. It will prevent the development of active tuberculosis in those infected, both while they take it and for many years (if not a lifetime) thereafter. The widespread and continued use of preventive therapy is our best hope of again decreasing the number of persons with active tuberculosis in the United States.

JONATHAN E. RODNICK, MD
San Francisco, California

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Zidovudine in the Treatment of Human Immunodeficiency Virus Disease

THE TREATMENT of human immunodeficiency virus (HIV) disease initially consisted of antimicrobial therapy for the opportunistic infections associated with the acquired immunodeficiency syndrome (AIDS). More recent research has been directed at developing a means of controlling the progression of infection by the virus itself. Zidovudine (AZT) is a thymidine analogue that inhibits HIV viral replication by interfering with the function of the viral reverse transcriptase.

Researchers reported the results of a placebo-controlled trial of zidovudine in adults with AIDS or severe AIDS-related complex. At a dose of 1,500 mg of zidovudine per day, there was a statistically significant decrease in mortality and the frequency of severe opportunistic infections that persisted for 18 months. Hematologic side effects were seen and included severe anemia and neutropenia.

The recent AIDS Clinical Trial Group Study examined the use of zidovudine in asymptomatic adults infected with HIV who had a CD4 cell count below 0.5×10^9 per liter (500 per μl). People were assigned to one of three treatment groups: those receiving placebo, 500 mg of zidovudine per day, or 1,500 mg of zidovudine per day. There was significantly less progression to AIDS or advanced AIDS-related complex in the two zidovudine treatment groups compared with the placebo group. There was no advantage to the higher dose of zidovudine in preventing the progression of HIV disease. The high-dose zidovudine group had the known hematologic side effects of anemia and neutropenia. These were not seen in the low-dose or placebo groups. The only side effect that was unique to the low-dose zidovudine group was nausea. The use of zidovudine in HIV-infected persons with CD4 counts greater than 0.5×10^9 per liter is under investigation.

These are important clinical findings in light of the fact

that most HIV-infected persons are currently asymptomatic. Primary care providers are in a position to identify persons who may benefit from the prophylactic use of zidovudine by offering HIV testing to their patients. The Food and Drug Administration has recently approved the use of zidovudine therapy (500 mg per day in five 100-mg doses) in persons with CD4 cell counts below 0.5×10^9 per liter. Patients receiving 500 mg per day of zidovudine should be monitored monthly with complete blood counts. Hemoglobin levels of less than 4.96 mmol per liter (8 grams per dl) or neutropenia, or both, indicate serious hematologic complications and may require discontinuation of the medication or a reduction in medication dose.

Questions remain regarding the long-term use of prophylactic zidovudine. The long-term side effects, the impact on survival, and the clinical significance of possible drug resistance are not known. Despite these uncertainties and the relatively high cost of zidovudine therapy, the minimal side effects with a 500-mg-per-day dose and the apparent delay in disease progression to AIDS make the use of zidovudine prophylaxis a serious consideration for asymptomatic HIV-infected persons with CD4 lymphocyte counts below 0.5×10^9 per liter.

MARIANNE A. McKENNETT, MD
San Diego, California

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Advances of the United States Preventive Services Task Force in Health Promotion and Disease Prevention

HEALTH PROMOTION and disease prevention are important aspects of family practice. Over the years, many opinions and recommended guidelines have been promulgated, but it has always been left up to individual practitioners to decide which interventions to use. In 1984 the US Department of Health and Human Services convened a special working group, the US Preventive Services Task Force. This group worked collaboratively with the Canadian Task Force on the Periodic Health Examination, which had previously done extensive work in the area. The result of this collaborative effort is the first set of truly comprehensive guidelines on the subject: the *Report of the US Preventive Services Task Force: Guide to Clinical Preventive Services.*

This guide synthesizes four years of extensive review of existing medical literature and interviews with numerous experts on preventive services. It contains recommendations on 169 screening, counseling, and immunization interventions for the prevention of 60 different common illnesses and conditions. Among the topics covered are cholesterol, coronary artery disease, breast and other cancers, prenatal disorders, nutrition, low back injury, dental disease, childhood and adult immunizations, chemoprophylaxis after exposure to various infections, smoking, alcohol abuse, and motor vehicle injuries.

The scientific basis for each intervention is evaluated in the following areas: "burden of suffering" (incidence, prevalence, morbidity, and mortality); "efficacy of screening tests" (sensitivity, specificity, predictive value, and reproducibility); and "effectiveness of early detection" (availability of "clinical interventions which can prevent or delay progression of the disorder"). For example, in the area of colorectal cancer, the task force neither endorses nor discourages screening, noting that despite the high burden of suffering, the efficacy of available screening methods is suboptimal and the effectiveness of early detection is not conclusively proved. It recommends screening for high-risk persons.

In other controversial areas, the task force also takes a middle-of-the-road position. In contrast to the 1988 recommendations of the National Cholesterol Education Program Expert Panel in which cholesterol screening is recommended every five years for all adults older than 20 years, the task force's recommendation is for "periodic screening" of middle-aged men. The task force mentions the expert panel's recommended frequency of every five years and states that it may be "clinically prudent" to screen others as well. The task force's "suggested threshold" for drug therapy is higher than the 1988 panel's recommendations, namely, a cholesterol level of 6.21 mmol per liter (240 mg per dl) in high-risk patients and 6.85 mmol per liter (265 mg per dl) in patients with no risk factors, versus 5.17 mmol per liter (200 mg per dl) and 6.21 mmol per liter, respectively. The task force's reasoning is that the effect on coronary artery disease of drug therapy in persons other than middle-aged men with levels of 6.60 to 6.85 mmol per liter (255 to 265 mg per dl) has not yet been proved; therefore, the potential risks and costs are not justified.

In the area of breast cancer screening, the task force's recommendations are also slightly different from previously published guidelines. In contrast to the 1987 and 1988 recommendations of the American Cancer Society and the National Cancer Institute, the task force recommends annual breast examination for all women beginning at age 40 and mammography every one to two years beginning at age 50. The recommendation for Pap testing is similar to the 1988 consensus statement adopted by the American Cancer Society, the American Academy of Family Physicians, and others, except for the addition of a recommended discontinuation at age 65 in women with previously normal Pap smears.

The recommended use of all of the interventions is summarized in a series of tables grouped according to age, sex, and other risk factors. Each table is appended with footnotes that detail the high-risk conditions for which certain interventions should be applied. Also listed in each table are the leading causes of death for each group, such as motor vehicle crashes, homicide, and suicide in teenagers; additional preventive services to be considered; and items to "remain alert for"—such as depression, abuse and neglect, and dental disease in the elderly.

Several important conclusions and implications emerged from the task force's review of existing evidence. First is that the most important contributors to preventable morbidity and mortality are the personal health behaviors of smoking, alcohol use, poor nutrition, and physical inactivity. The implication of this is that interventions which address these behaviors, namely counseling and patient education, may have a more valuable effect than the conventional ordering of tests. Further, as the locus of responsibility for personal health

practices necessarily shifts onto patients, physicians will need to use appropriate communication skills to help empower patients to change their behaviors.

Finally, the task force's review pointed out the inadequacy of existing data. Either studies were completely lacking in some areas, or existing studies were nonconclusive due to improper study design. This points out a vital area of research in which family practice could make a significant difference. The task force guide can be obtained by calling 1-800-638-0672 and asking for publication No. 97913-0.

SADHNA K. KHALSA, MD
Los Angeles, California

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Pap Smear Update—The Bethesda (Nomenclature) System

THE PAPANICOLAOU smear deserves credit for the significant decline in the incidence of invasive cervical cancer in screened populations. Despite the wide adoption of this screening tool in the United States since its introduction in the 1940s, however, 7,000 women per year continue to die of this theoretically preventable disease. Related Pap smear issues currently being studied and reported in the literature include risk factors for cervical carcinoma (including human papillomavirus); the cost-effective frequency of screening (the US recommendation for every one to three years is related to risk factors and personal Pap smear history); improving the access to screening for low-income, high-risk populations; specimen collection techniques, such as cytobrush for nonpregnant endocervical cell sampling; laboratory quality assurance, including uniform and clinically relevant interpretation and reporting of results; and the appropriate clinical management of inadequate and abnormal specimens.

In December 1988, the National Cancer Institute convened 51 experts from the disciplines of pathology, cytology, and obstetrics and gynecology in Bethesda, Maryland, to address the last two issues. The participants unanimously agreed to view the Pap smear report as a medical consultation (improved by adequate clinical data) and to adopt the Bethesda System as the preferred nomenclature for cervical and vaginal cytopathology reporting.

The Bethesda System introduces two new, inclusive, descriptive terms: *low-grade* and *high-grade squamous intraepithelial lesion.* Previous nomenclatures, felt to be nonspecific and not reproducible, have been absorbed into the two larger categories. Low-grade squamous epithelial lesion is the new designation for the former mild dysplasia, cervical intraepithelial neoplasm, or CIN 1, and cellular changes associated with human papillomavirus. High-grade squamous epithelial lesion encompasses *moderate dysplasia* to *carcinoma in situ,* or CIN 2 to CIN 3. *Atypia* is now used to describe only changes of undetermined significance—that is, not inflammation.

The new report format would include the following:

- A statement of specimen adequacy—satisfactory, less than optimal, or unsatisfactory;
- A general categorization of diagnosis—within normal limits or other—to facilitate clinical triage; and
- A descriptive diagnosis—infection and type, reactive or reparative changes, epithelial cell abnormalities, nonepithelial malignancy, hormonal evaluation, or other.

When results are not within normal limits, or when specimens are unsatisfactory, the report should include clinical recommendations for follow-up by the reporting cytologist.

The Bethesda System attempts to clarify the Pap smear screening diagnosis and to exploit the consultant role of the cytologist. The objective is to facilitate the appropriate clinical investigation and early intervention for which Pap smear screening is intended.

DEBORAH M. PIPER, MPH, CNM
San Diego, California

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Nonpharmacologic Management of Hypertension

MUCH OF THE IMPETUS for promoting nondrug approaches to control blood pressure stems from the risks associated with medication use, especially among mildly hypertensive patients. This also presents an opportunity to modify associated risk factors in susceptible persons. The 1988 Report of the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure recommended that nonpharmacologic approaches be used both as definitive intervention and as an adjunct to drug therapy.

The recommendation to reduce sodium intake has become a practice standard for blood pressure control. The average American diet contains about 10 to 20 grams of salt per day (170 to 350 mEq of sodium). Moderate sodium restriction has been shown to reduce systolic blood pressure by an average of about 10 mm of mercury and the diastolic pressure by about 5 mm of mercury. It is important to note that the effect of this restriction is not universal. Some patients—for example, African Americans and the elderly—are more salt-sensitive than others.

The incidence of hypertension among obese persons is 50% greater than among those with normal body weight. In past studies, weight loss has resulted in a substantial lowering of blood pressure.

Controversy exists regarding the role of low levels of potassium, magnesium, and calcium in the development and maintenance of hypertension. Nevertheless, it would be prudent to maintain adequate levels of these important cations.

Vegetarians and persons with a diet high in polyunsaturated fats have been shown to have lower blood pressures than those with a diet high in saturated fats and low in polyunsaturated fats. Recently it was shown that ingesting 50 ml of fish

oils per day for two months resulted in an average decline of 6.5 mm of mercury systolic and 4.5 mm of mercury diastolic blood pressure in hypertensive persons. These studies provide further impetus for recommending a heart-healthy diet.

Because ingesting more than 1 oz of alcohol per day may be responsible for a large percentage of hypertensive patients seen in family practice, limiting alcohol intake is an important recommendation.

The direct benefits of exercise on blood pressure control are difficult to isolate from those of the changes that often accompany exercise, such as improved diet, weight loss, and decreased cigarette smoking. Considerable evidence suggests, however, that regular aerobic exercise by itself does effectively reduce blood pressure. Declines in mean diastolic blood pressure from 117 to 97 mm of mercury have been documented after just three months of daily walking or running 3 km (2 mi).

Life-style changes should be encouraged to forestall, minimize, or obviate the need for medication. One study showed that by reducing weight, salt, and alcohol intake, 39% of patients with less severe hypertension previously controlled with medication remained normotensive for four years without requiring any medication.

Using a nonpharmacologic approach to hypertension is an important adjunct for controlling blood pressure. Benefits may include not only reducing the need for medication, but also improving the subjective perception of well-being and increasing quality of life. It is important, however, to monitor the progress of patients placed on a nondrug regimen. If the diastolic blood pressure remains above 90 mm of mercury after employing nonpharmacologic measures for at least six months, then drug therapy should also be considered.

STEPHEN BRUNTON, MD
Long Beach, California

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A New Treatment of Nocturnal Enuresis

ALTHOUGH 2 to 3 million children nationwide suffer some degree of distress because of nocturnal enuresis (bed wetting), there continues to be controversy as to its origin and treatment. Enuresis is defined as a lack of bladder control in a child who has reached an age when urinary control is usually expected. Although most children have achieved control by 4 years of age, some 10% of 6-year-old children and 2% of 14-year-olds have nocturnal enuresis. There is evidence that heredity plays a role, but separating genetic characteristics from family expectations is difficult. The differential diagnosis includes infection, neurogenic urinary bladder, diabetes mellitus, urinary tract anomalies, and emotional problems. Enuresis is primary if bladder control has never been completely present and secondary if urinary incontinence has not occurred for a prolonged period (six months or more). While secondary enuresis is likely to be associated with an underlying illness, infection, or psychosocial stress, the overwhelming majority of cases of primary enuresis are not associated with any of the forementioned causes.

Although studies show that the functional bladder capacity of enuretic children is smaller than that of nonenuretic children, their daytime bladder function is basically normal. Thus, the role of functional capacity is unclear. Conventional therapies for children affected with nocturnal enuresis include setting alarm clocks to awaken the child to go to the bathroom, a regimen of imipramine hydrochloride, and moisture alarms. Unfortunately, some children are only partially helped, and results are less than satisfying to physicians, patients, and parents alike.

Recent studies in Denmark indicate that enuresis may be directly related to an insufficient secretion of antidiuretic hormone (ADH) at night, resulting in a nighttime overproduction of urine. Normal children were found to regulate urine production by increasing ADH levels at night. Enuretic children, however, did not have an increase in ADH levels and produced an abnormally large volume of urine that resulted in bed wetting. Enuretic children were also found to urinate with a full bladder, and, in some cases, were found to repeatedly fill their bladder throughout the night. Having identified these striking physiologic changes in enuretic children, researchers successfully used desmopressin acetate nasal spray (DDAVP), a synthetic ADH, to decrease urine output and stop the enuresis. These early studies led to subsequent well-controlled, double-blind clinical trials that have confirmed that DDAVP is effective in controlling nighttime urine production.

Desmopressin acetate is currently available in a nasal spray pump and has been approved by the US Food and Drug Administration for the treatment of primary nocturnal enuresis. The nasal spray is applied directly to the nasal mucosa, and the dosage should be adjusted according to the individual response. The recommended initial dose for children who are 6 years of age and older is 20 μg (0.2 ml solution) at bedtime, though some patients may respond to less medication. Adjustments up to 40 μg are suggested if there is no response. The manufacturer recommends that half of the dose be administered in each nostril. Side effects are usually mild and are limited to mucosal irritation, with occasional dose-related gastrointestinal upset. Serum electrolyte levels should be checked if therapy is continued beyond seven days.

Although patients have been kept on the medication therapy for extended periods of time, no adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have been conducted beyond four to eight weeks. The high cost of the medication (more than $60 per month) is a limiting factor to a widespread application of this treatment approach. At the same time, the fact that many people are willing to pay this much for the medication underscores the level of emotional distress that some patients and families experience as a result of nocturnal enuresis.

WILLIAM L. TOFFLER, MD
FRANKLIN WEINGARTEN, MD, PhD
Portland, Oregon

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Progestin-Only Contraception

PROGESTIN-ONLY CONTRACEPTIVE methods work by altering the cervical mucus, making it thick and scanty so that it is more difficult for sperm to penetrate; by affecting motility of the oviduct and uterus, thus affecting ova and sperm transport; and by altering the endometrium so that less glycogen is available for blastocyst survival. Ovulation may be inhibited as infrequently as 10% of the time. The progestin-only pill, used in England for years, has a failure rate of 1% to 2.5%. Although intermittent irregular bleeding is a frequent side effect, the progestin-only pill is especially useful for a woman who is breastfeeding or who has estrogen-related side effects, such as chloasma, using the combined pill. Injectable progesterone is used worldwide, but its use has not been approved in the United States, primarily because mammary tumors developed in beagle dogs during experimental testing; this work is being repeated. Vaginal rings and intrauterine devices that release progesterone have also been developed.

Recently approved by the Food and Drug Administration is the levonorgestrel implant, Norplant, which releases 50 to 80 μg of levonorgestrel daily in the first year, then 30 to 35 μg in subsequent years. With this progestin-only method, ovulation is inhibited in at least 50% of cycles. Using a trochar, six matchstick-size silastic capsules are placed under the skin of the upper inner arm. It is effective for five years and has a 98.5% effectiveness rate. Side effects include irregular menstrual bleeding (60% to 70%) and headaches (5% to 20%). Placement takes about 15 minutes and is easier than removal because over time, fat and fibrous tissue can develop around the capsules. A new system, Norplant-2, is being developed that would use only two capsules, provide the same efficacy, last for three years, and, because of requiring fewer capsules, be easier to insert and remove. It is likely that Norplant will soon be replaced by Norplant-2.

Next on the horizon is a biodegradable progestin-only implant. One form will be norethindrone in cholesterol. It is not clear how easy these will be to remove in a patient with severe bleeding or if a patient requests removal. In fact, recent data indicate that it will not be possible to remove them.

There are several questions and concerns with the progestin-only methods. One is the common side effect of irregular bleeding, which leads 12% to 19% of women to discontinue the levonorgestrel implant. Levonorgestrel is one of the more androgenic progestins currently marketed in the United States, and, although the capsules release a low dose, the potential may exist for side effects such as those seen with androgenic progestins in the oral contraceptive pill, for instance, acne, hirsutism, and depression. Clinical trials have shown an incidence of acne of 5% to 20% and have not reported the other side effects. Although initial trials of the levonorgestrel implant have demonstrated a drop of 5% to 15% of both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels, longer term studies of its effect on lipids will be necessary because it is known that the progestin component of the combined pill tends to increase LDL levels and decrease HDL levels. Finally, recent studies in macaque monkeys show that progestin-only contraception was more likely to cause atherosclerosis than balanced estrogen-progestin contraception.

On the one hand, the levonorgestrel implant will be a useful method for women who find it difficult to comply with other contraceptive options and who want an effective method. On the other hand, side effects may lead many women to have them removed.

ELLEN BECK, MD
San Diego, California

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Pregnancy Testing—Home and Office

THE RAPIDLY CHANGING TECHNOLOGY for pregnancy tests has greatly enhanced our ability to confirm early pregnancy not only in the office or laboratory setting but also in the home. Home pregnancy tests were first marketed in the 1970s, and they have been increasingly accepted (used by about 30% of pregnant women) despite concern regarding their accuracy. The first home pregnancy test, "ept," did not require Food and Drug Administration (FDA) approval. The FDA has judged all subsequent products to be "substantially equivalent," thus free from regulation. While manufacturers claim 98% to 99% accuracy as early as six days after the missed menses, one study resulted in a positive predictive value of only 65.5% for pregnancies of nine days or less from the missed menses.

Until recently, most office pregnancy tests were latex agglutination inhibition tests or hemagglutination inhibition tests (performed using either slide or tube techniques). These have generally been replaced by monoclonal antibody tests, which are more sensitive and specific. Latex agglutination inhibition slide tests are positive with human chorionic gonadotropin (hCG) levels of 1,500 to 3,500 IU per liter 38 to 42 days after the last menstrual period. Latex agglutination and hemagglutination inhibition tube tests are slightly more sensitive, turning positive with hCG levels of 750 to 850 IU per liter 35 days after the last menstrual period.

Monoclonal antibody tests are far more sensitive, turning positive with hCG levels of 20 to 50 IU per liter 24 to 27 days after the last menstrual period. Urine is placed on a membrane with anti-α monoclonal antibodies; hCG in the urine binds to the membrane. A solution is added that reacts with the β-subunit, creating an antibody-hCG-antibody complex. This second antibody attaches to the complex, creating a blue dot, which indicates a positive test. While monoclonal antibody tests are usually done using urine, they are also available using serum (accurate even with hCG concentrations as low as 10 IU per liter). An extra step is required to achieve this small increase in sensitivity, which is seldom of clinical relevance compared with urine tests.

The percentage of positive tests at 13 days and 16 days after ovulation (documented by ultrasonography) or follicular aspiration is 75% and 100%, respectively, for "FACT," 60% and 75% for "Daisy 2," and 95% and 95% for "Advance." FACT and Daisy 2 use monoclonal antibodies that detect hCG in urine with a hemagglutination inhibition assay. Advance uses monoclonal antibodies that assist enzymes specifically to detect hCG.

The reliability of any test depends on the experience and competence of the user. Home tests have been significantly more accurate when used by older patients or those with higher incomes. The false-negative rate when used at a family planning clinic is lower (16.7%) than when used in a private office (21.1%) or a general public clinic (40.0%).

Monoclonal antibody testing now available for home and office will assist in earlier diagnosis. To improve accuracy, unless medically imperative, patients should be encouraged to wait longer than the six to nine days after the missed menstrual period that manufacturers recommend. Patients must be instructed in the proper technique, including the use of a morning's first urine. When used appropriately, home pregnancy tests enable patients to take increased responsibility for their own health care and minimize potential risks, such as exposure to drugs or irradiation during early pregnancy.

SCOTT A. FIELDS, MD
WILLIAM L. TOFFLER, MD
Portland, Oregon

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Immunization Update

MANY REVISED RECOMMENDATIONS for routine immunizations for children, adults, and certain high-risk groups have been published recently. For example, there are now new immunizations for children, and the schedule for routine immunizations has changed. The recent measles epidemic stimulated new recommendations for immunizing adults against measles. There are also new recommendations for certain high-risk groups, such as health care workers and patients with human immunodeficiency virus (HIV) infection.

Children

Originally the *Haemophilus influenzae* type b (Hib) vaccine was recommended for high-risk children at 18 months and all other children at 2 years of age. One *H influenzae* b conjugate vaccine (HibTITER, Lederle) is now available. This new immunization should be given at the 2-, 4-, and 6-month visits (with the oral attenuated poliovirus vaccine [OPV] and diphtheria and tetanus toxoids with pertussis vaccine [DTP]) with a booster at 15 months. Prophylactic acetaminophen administration decreases the systemic side effects of the DTP immunization in children. Other conjugated vaccines may soon be shown to be safe and effective for administration before 15 months of age. Measles immunization continues to be given in combination with mumps and rubella (MMR). Until recently they were given only at 15 months, but now they are given at both 15 months and 4 to 6 years. In areas of high risk, the MMR-1 should be given at 12 months of age. Finally, the 6-month dose of OPV can now be dropped in low-risk areas.

Adults

The influenza vaccine continues as a standard of medical practice to be considered for those with severe medical conditions (especially heart and lung disease), those older than 65, nursing home residents, immunocompromised patients (including people with the acquired immunodeficiency syndrome), and health care workers. All adults older than 65 years and patients with certain chronic medical conditions should receive the pneumococcal vaccine one time. Recent reports that at least 40% of persons 60 years of age and older are not adequately immunized against diphtheria and tetanus should lead to an increased use of the dT immunization.

Special Groups

Three groups deserve special attention. First, all health care providers, especially if they come in contact with bodily fluids, should consider the three-part immunization against hepatitis B. Travelers should contact a local traveler's clinic or the health department at least two months in advance to learn which immunizations are required and recommended for their trip. Finally, those with HIV infection should be up-to-date with their immunizations, especially dT and pneumococcal and possibly measles and influenza. Avoid the OPV vaccine in these immunocompromised patients; the trivalent enhanced-potency, inactivated poliovirus vaccine (IPV) is recommended instead.

A new system was started last year for physicians to report adverse reactions to vaccines. Further information on the Vaccine Adverse Event Reporting System (VAERS) is available 24 hours a day at 1-800-822-7967.

THEODORE G. GANIATS, MD
San Diego, California

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Intrauterine Devices and Pelvic Inflammatory Disease—A Reanalysis of the Literature

INTRAUTERINE DEVICES (IUDs) are used less and less as a form of contraception in America. This is probably because of decreased marketing due to the litigation related to the Dalkon Shield. Additional concerns with IUDs include side effects of discomfort, increased bleeding, and the traditional belief that IUDs contribute to an increased incidence of pelvic inflammatory disease. There are two IUDs currently available in the United States. The Progestasert must be replaced every year and has a higher rate of ectopic pregnancy than other IUDs. The ParaGard (copper T 380A), a copper IUD, has a failure rate of about 3% and can be left in place for four years at a time.

All IUDs have an increased risk of pelvic inflammatory disease in the first 30 days. This is probably because of contamination of the uterine cavity during insertion. Other causes may include that the tail of the IUD allows bacteria to rise up the cervix and that the IUD will cause local inflammation in the area where it rests. For years, however, a belief has prevailed that IUD use leads to an increased risk of pelvic inflammatory disease after the first 30 days as well. This belief has recently been called into question. In cohort or prospective studies of women with IUDs, the risk of pelvic inflammatory disease was similar to that in sexually active women in industrial countries—about 1% to 2% in the 1970s. In a review of 17 case-control studies, it was found that these studies had often not corrected for oral contraceptive pill use in controls—that is, contraceptive pill use in controls may have provided protection from pelvic inflammatory disease.

Those case-control studies that had 100% diagnostic accuracy (by using laparoscopy or laparotomy) and that corrected for oral contraceptive use show no or borderline statistical significance. In the remaining case-control studies after 1973, once there had been a great deal of publicity about the link between IUD use and pelvic inflammatory disease, both diagnostic bias (inflammatory disease being overdiagnosed in women presenting with abdominal pain who had an IUD in place) and referral bias may have skewed the data. Referral bias implies that the cases of pelvic inflammatory disease studied may not have been representative of all women with the disease. Women who had an IUD in place and had symptoms of pelvic inflammation were more likely to be referred by community physicians to a hospital. In the hospital, they were more likely to be included in studies than women in the community who had pelvic inflammatory disease but no IUD in place. Thus, women with pelvic inflammatory disease and an IUD in place may have been overrepresented in studies of risk factors leading to the disease.

This reevaluation of the data supports the position of a review of IUDs published in April 1989 in which the authors conclude that the IUD *can* be an acceptable method of contraception—especially for those women who are in the middle to older reproductive years, unable to take oral contraceptives, and in a stable, monogamous relationship and thus at low risk for sexually transmitted diseases.

ELLEN BECK, MD
San Diego, California

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Physical Activity in Primary Prevention

IMPORTANT CHANGES concerning exercise intervention were confirmed with the 1989 recommendations of the US Preventive Services Task Force. The task force gave the same recommendation for counseling patients for physical inactivity as it gave for cigarette smoking and high blood pressure. Physical inactivity has long been recognized as a risk factor in coronary heart disease (CHD), but many physicians have felt it to be relatively unimportant compared with other risk factors such as cigarette smoking and elevated blood pressure. Recent studies have indicated that those who are not physically active have roughly the same risk of CHD developing as those with hypertension, hypercholesterolemia, or those who smoke. The strength of the association between physical inactivity and CHD is 1.9 compared with 2.1 for high systolic blood pressure, 2.4 for elevated serum cholesterol level, and 2.5 for smoking.

Researchers have found that physical fitness is associated with lower rates of all causes of mortality as well as CHD and cancer mortality. Further, the greatest reduction in relative risk occurred between the lowest level of fitness and the next lowest level. These data suggest that even modest improvements in fitness levels among the most unfit can result in substantial health benefits.

Counseling of physically inactive patients should emphasize regular, mild-to-moderate activity, such as brisk walking. More strenuous exercise activities should be de-emphasized. In the past, exercise prescriptions typically suggested relatively intense activity, such as jogging, for 20 minutes at least three times per week. The task force now recommends that all patients should be counseled to engage in regular physical activity in a program tailored to their health status and life-style. Beginning exercisers should start with a regular, low to moderate level of exercise. Their goal should be to engage in an activity like brisk walking at least three times per week for at least 30 minutes.

Screening and intervention with physically inactive patients should specifically be included in periodic health examinations of all adults. A 1978 Harris survey found that most people reported they would be more likely to engage in health-promoting behavior if the recommendations came from their physician rather than from any other source. Inactive patients are most likely to comply with recommendations from their physicians for a regular pattern of exercise activity that can be maintained with minimal disruption of other aspects of their lives. Walking, when done briskly, is the ideal activity that meets these recommendations and can serve as a first step to more vigorous activities, if desired, in the future.

ALLAN V. ABBOTT, MD
Los Angeles, California

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Santa Monica

Alerts, Notices, and Case Reports

Treatment of Adult Systemic Cat Scratch Disease With Gentamicin Sulfate

DREW E. LEWIS, MD
MARK R. WALLACE, MD
San Diego, California

CAT-SCRATCH DISEASE, typically benign and self-limited, is the most common cause of chronic regional lymphadenitis in children. The causative gram-negative bacillus[1] is usually inoculated into the patient from the scratch of a kitten. While usually benign, the disease can be chronic and severe.[2] Whether cat-scratch disease responds to antibiotic therapy is unclear,[3] although gentamicin therapy has been reported to be effective in severely affected children.[4] We report the case of a patient with prolonged and debilitating cat-scratch disease for whom gentamicin therapy provided a rapid clinical response.

Report of a Case

About 3½ weeks before being seen, the patient, a 49-year-old man, was scratched on his distal right arm by a 3-week-old kitten. Nine days later, pustular eruptions appeared over the scratch marks, followed several days later by persistent fever (as high as 40°C), daily afternoon rigors, and a painful axillary mass. At the time of evaluation he had experienced these symptoms for 12 days. The rest of the medical history was not relevant.

On physical examination, he was febrile (39.0°C) and had a 2- by 3-cm soft, fluctuant, exquisitely tender lymph node in the right axilla and three scratches from the right wrist to the mid-forearm. Three pustules, each on an erythematous base, were located on two of the scratches. No epitrochlear or other adenopathy was present. The leukocyte count was 8.5×10^9 per liter (8,500 per μl), hemoglobin 7.45 mmol per liter (12.0 grams per dl), platelets 210×10^9 per liter (210,000 per μl), and erythrocyte sedimentation rate 57 mm per hour; values for electrolytes, blood urea nitrogen, creatinine, liver-associated enzymes, and urinalysis were normal. Gram's stain of one pustule's contents revealed many polymorphonuclear leukocytes, but no organisms were seen or grown on routine media after seven days' incubation. Serologic studies were negative for *Brucella* species, tularemia, coccidioidomycosis, and toxoplasmosis.

A regimen of intravenous gentamicin sulfate was started at a dose of 5 mg per kg of body weight per day. Within 16 hours the patient's temperature returned to normal and his axillary node was much smaller and less tender. Gentamicin concentrations were measured after a steady state was achieved and showed a peak of 6 μg per ml and a trough of 1.3 μg per ml. After five days of therapy, he was discharged without axillary adenopathy or constitutional symptoms. A cat-scratch antigen test was positive (5 mm) at 48 hours and was 10 mm at seven days.* When reevaluated 16 weeks later, the patient had remained well.

Discussion

In 1950, a Parisian pediatrician, Robert Debré, described regional adenopathy sometimes associated with fever following a scratch from a cat or, more frequently, a kitten. First observed in 1931,[5] this syndrome remained of uncertain etiology until 1983 when a delicate pleomorphic gram-negative bacillus was identified in the lymph nodes of 34 patients.[1] Other groups have confirmed this finding.[6-8] Bacteria isolated from the lymph nodes of patients with cat-scratch disease are capable of producing lesions in armadillo skin identical to the early lesions seen in humans, and the bacterium can then be isolated from these skin lesions, fulfilling Koch's postulates.[8]

This common disease in children usually presents as tender regional adenopathy.[9] Unusual manifestations include the oculoglandular syndrome of Parinaud,[10] encephalopathy,[9] osteolytic lesions,[9] thrombocytopenic purpura,[9] atypical pneumonia,[9] granulomatous hepatitis,[11] pleural effusions,[12] splenic abscess,[13] synovitis,[2] proteinuria,[9] and a severe chronic systemic disorder.[2] Treatment is rarely needed in the typical case. The presence of one of the complications or of a prolonged course, however, may require treatment. Convincing descriptions of the response of cat-scratch disease to an antibiotic regimen containing an aminoglycoside have been published for an adult recipient of a renal allograft[4] and for three children with severe disease.[5] These clinical responses to aminoglycosides are consistent with in vitro antimicrobial susceptibility studies.[8] In our patient, the use of gentamicin rapidly resolved the signs and symptoms that had been present continually for 12 days.

We conclude that in complicated cases of cat-scratch disease, the parenteral administration of gentamicin is a reasonable and effective treatment. Its use should be considered on an empiric basis for chronic or life-threatening infection due to the cat-scratch bacillus until randomized trials can be conducted.

*A. M. Margileth, MD, provided the cat-scratch antigen.

(Lewis DE, Wallace MR: Treatment of adult systemic cat scratch disease with gentamicin sulfate. West J Med 1991 Mar; 154:330-331)

From the Departments of Internal Medicine (Infectious Disease) and Clinical Investigation, Naval Hospital, San Diego, California.

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Reprint requests to LCDR D. E. Lewis, MC, USNR, c/o Clinical Investigation Department, Naval Hospital, San Diego, CA 92134-5000.

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The Cardiovascular Manifestations of Leptospirosis

ANDREW C. DIXON, MD
Chicago, Illinois

LEPTOSPIROSIS is an uncommon zoonosis caused by any of the almost 170 serotypes of the spirochete *Leptospira interrogans*. Most commonly associated with tropical climates, this disease has been reported from all regions of the United States and most of the world. Most persons infected with this organism have either subclinical disease or a mild anicteric febrile illness, but 5% to 10% of patients will have severe leptospirosis, characterized by jaundice and azotemia. This subset of severely ill patients has what has been called Weil's disease after the physician who first described this illness in 1886.

Previous studies of patients with severe leptospirosis have usually focused on the hepatic and renal manifestations of this illness. Despite the fact that as many as 10% of patients may have associated cardiac involvement,[1,2] these manifestations are seldom discussed in reviews on the clinical aspects of this disease. I describe the case of a patient in whom severe leptospirosis developed with several cardiac changes. A review of both the clinical and pathologic literature that has addressed the many cardiac manifestations of this uncommon disease is also presented.

Report of a Case

The patient, a 42-year-old man, was transferred to a Honolulu, Hawaii, hospital from a rural hospital on a neighboring Hawaiian island where he had been admitted for the treatment of a febrile illness characterized by spiking fevers to 40°C (104°F), severe myalgias, and some mild hallucinations. At that hospital he had been noted to have fever, jaundice, mild hypotension, and thrombocytopenia and had been treated with intravenous penicillin and oral tetracycline therapy for presumed leptospirosis. He was transferred when no improvement was noted by the second hospital day.

The patient said he had no significant travel history or unusual exposures. He had been in good health and was employed as a police officer and part-time construction worker. On physical examination the patient appeared flushed and jaundiced. The temperature was 39.9°C, the pulse rate 140 beats per minute, and the respiratory rate 36 per minute. An initial systolic blood pressure of 80 mm of mercury rose after a fluid bolus. There was a varicelliform rash over the face and neck, and right axillary adenopathy was noted. Bilateral conjunctival suffusion was present. There was no jugular venous distention, and the lungs were clear. Examination of the heart disclosed a tachycardic rhythm and the presence of a third heart sound. The abdomen was normal with no hepatosplenomegaly. Other than severe proximal muscle tenderness, the rest of the examination elicited no abnormalities.

The hematocrit was 0.28, the platelet count was 66×10^9 per liter, and the leukocyte count was 13.5×10^9 per liter with 0.61 neutrophils, 0.34 band forms, 0.04 lymphocytes, and 0.01 mononuclear cells.* Prothrombin and partial thromboplastin times were normal. The blood urea nitrogen level was 8.9 mmol per liter (25 mg per dl; normal, 3.0 to 6.5 mmol per liter); serum creatinine, 195 μmol per liter (2.2 mg per dl; normal, 50 to 100 μmol per liter); total bilirubin, 202 μmol per liter (11.8 mg per dl; normal, 2 to 18 μmol per liter); lactate dehydrogenase, 265 units per liter (normal, 50 to 150); and creatine kinase, 5,914 units per liter (normal, <130). Arterial blood gas measurements with the patient receiving supplemental oxygen showed a pH of 7.47, a P_{CO_2} of 31 mm of mercury, and a P_{O_2} of 119 mm of mercury. An electrocardiogram showed sinus tachycardia with an intraventricular conduction delay and diffuse, nonspecific T-wave changes (Figure 1). A chest roentgenogram showed mild cardiomegaly and diffuse bilateral interstitial infiltrates (Figure 2). Catheterization of the right side of the heart revealed a pulmonary capillary wedge pressure of 13 cm of water, a cardiac output of 7.09 liters per minute, and a calculated systemic vascular resistance of 699 dynes·sec·cm². A Gram's stain of the cerebrospinal fluid was negative for organisms.

Serum and urine specimens were obtained for bacterial, viral, and leptospiral cultures and serologic tests, and the patient was treated with intravenous penicillin, doxycycline, and an ampicillin-sulbactam sodium combination. On the second day of admission a bedside echocardiogram showed a mildly dilated left ventricle with an end-diastolic diameter of 5.8 cm. The overall systolic function was mildly depressed with no segmental wall motion abnormalities detected. The shortening fraction was 25%, and a small posterior pericardial effusion was seen.

By the third hospital day the patient noted diminished myalgias and improved strength; at this time the total bilirubin concentration had risen to 279 μmol per liter, but the creatine kinase level had begun to fall. Over the next week the hyperbilirubinemia and elevated creatinine levels returned to normal, the pulmonary infiltrates resolved, and the third heart sound disappeared. The patient was discharged on his ninth hospital day. At the time of discharge all cultures, including both blood and urine for leptospirosis, remained neg-

ABBREVIATIONS USED IN TEXT
ARDS = adult respiratory distress syndrome
ECG = electrocardiogram

*For hematocrit and differential cell count, the values are expressed as a fraction of 1.

(Dixon AC: The cardiovascular manifestations of leptospirosis. West J Med 1991 Mar; 154:331-334)

From the Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu. Dr Dixon is currently with the Division of Critical Care Medicine, Department of Medicine, Rush-Presbyterian-St Luke's Medical Center, Chicago, Illinois.

Reprint requests to Andrew C. Dixon, MD, Div of Critical Care Medicine, Dept of Medicine, Rush-Presbyterian-St Luke's Medical Center, Jelke 1021, 1653 W Congress Parkway, Chicago, IL 60612.

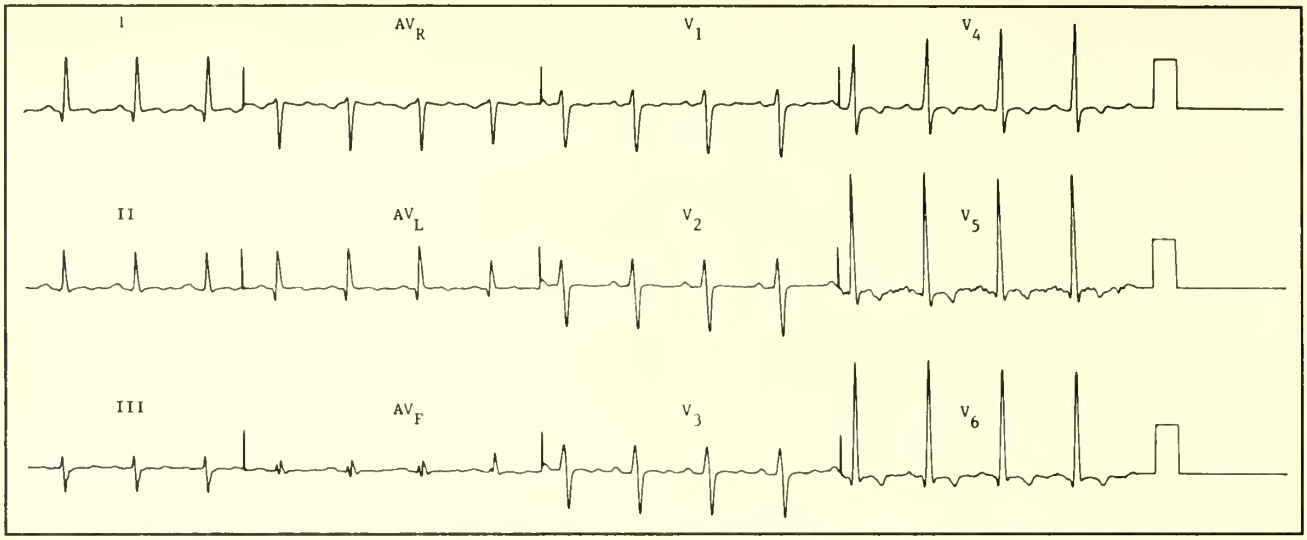

Figure 1.—The electrocardiogram of a patient with leptospirosis shows an intraventricular conduction delay and nonspecific ST-T wave changes.

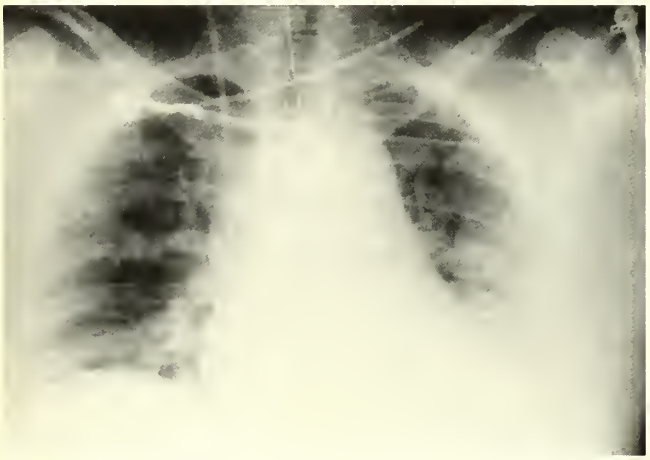

Figure 2.—A chest roentgenogram of a patient with leptospirosis shows cardiomegaly and diffuse bilateral infiltrates.

ative. A microscopic agglutination test for *Leptospira* antibodies was positive at a 1:800 dilution; over 1:100 is consistent with an acute infection. Titers for Rocky Mountain spotted fever, toxoplasmosis, adenovirus, coxsackievirus groups A and B, echovirus, and influenza virus groups A and B were negative for acute infection. Two days after discharge a follow-up echocardiogram showed resolution of the previous left ventricular dilatation and return of the systolic function to normal. The patient has since remained in good health.

Discussion

Leptospirosis, while uncommon, affects people of all age groups from all areas of the world. It is usually acquired through contact with either domestic or wild animals. Frequently exposure occurs from swimming or partial immersion in contaminated water sources. In Hawaii, leptospirosis is more common, and the most important vectors are thought to be rats, mice, and mongooses. Symptoms usually begin several days to several weeks after exposure and range from a mild febrile illness to overt Weil's syndrome with azotemia, jaundice, confusion, anemia, thrombocytopenia, and high temperatures. An aseptic meningitis may also result from infection with this organism.

The incidence of cardiovascular manifestations in patients with leptospirosis remains unknown. In 1951 Sodeman and Killough reported data from 80 patients with leptospirosis, of whom 8 (10%) had definite evidence of cardiac involvement.[1] Hospital-based studies have found even higher rates,[3,4] and postmortem studies have elicited histologic evidence of cardiac involvement in as many as 70% of patients dying of leptospirosis.[5,6] Common to all these studies is the presence of severe systemic disease, often with both renal and hepatic involvement (Weil's syndrome).

In outpatients with leptospirosis, cardiovascular manifestations are seldom observed.[7-9] These patients are usually anicteric and have a low prevalence of renal disease. The reasons why some patients have multiple systemic manifestations of leptospirosis while others remain asymptomatic are unknown.

The case of presumptive leptospirosis described herein illustrates several of the cardiac manifestations that have been associated with leptospirosis, including nonspecific electrocardiographic changes, both clinical and echocardiographic evidence of left ventricular dysfunction, and the development of a pericardial effusion.

Electrocardiographic Abnormalities

Numerous electrocardiographic (ECG) abnormalities have been found in patients with leptospirosis. In the case described, these represented delayed intraventricular conduction and diffusely inverted or flattened T waves (Figure 1). Both intraventricular conduction delay and nonspecific T-wave changes were reported in the study by Sodeman and Killough of 80 cases of Weil's disease.[1] Of their eight patients who had clinical evidence of myocardial involvement, seven had either flattened or inverted T waves on an ECG, most commonly in the anterior or lateral leads.[1] Another study of the ECG abnormalities of leptospirosis noted pronounced anterior ST-segment elevation in four patients.[10] In none of the patients in either study did clinical or laboratory evidence of myocardial infarction develop, and in cases where follow-up information was available, the ECG returned to normal after proper antibiotic therapy. In the latter series the authors postulated a localized myocarditis or pericarditis to explain these ECG findings.[10]

Other ECG changes have also been described. ST-T wave changes characteristic of pericarditis have been found in at least one patient with a leptospirosis-induced pericardial friction rub.[11] Delayed intraventricular conduction or bundle branch blocks have been reported in at least one review[1] but appear to be an infrequent finding. Even children have been found to have nonspecific ECG abnormalities in association with leptospirosis.[3]

Despite these sometimes dramatic changes, the sensitivity of an ECG for identifying myocardial involvement is not high. Of note, several patients with overt pulmonary edema and atrial arrhythmias have been reported to have otherwise normal ECGs.[4]

Arrhythmias

Rhythm disturbances also appear commonly in patients with leptospirosis. A relative bradycardia may be found in many of these patients.[12] The mechanism of this pulse-temperature discrepancy is unclear but has also been reported in association with other infectious diseases. Atrial arrhythmias, including both atrial fibrillation and atrial flutter, are frequently encountered.[3,4,12] Premature ventricular contractions are common, and one case of ventricular tachycardia has been reported.[13] A study of nine children with leptospirosis reported three to have suffered at least one cardiopulmonary arrest during their hospital stay.[3] The antecedent rhythms, clinical findings, and outcome of those three patients were not reported. In addition, both first- and second-degree heart block[14] and junctional rhythms[10] have been described in patients with leptospirosis.

As with the ECG abnormalities, rhythm disturbances associated with leptospirosis usually resolve early in the course of the illness.

Pericarditis

Although leptospirosis-induced pericarditis has been reported in several studies,[11,15-17] the etiology and prevalence remain unclear. The diagnosis has usually been established by the presence of a pericardial friction rub or ECG findings, or both, characteristic of pericarditis. Because of the high incidence of severe renal disease in these patients, the distinction between uremic pericarditis and that which is the direct result of leptospirosis may at times be difficult.[12] Studies correlating the clinical and pathologic findings in these patients have not yet been done.

Congestive Heart Failure

Several authors have described clinical evidence of congestive heart failure in patients with leptospirosis, but this also appears to be an infrequent complication.[1,3,10,13] Studies as early as 1917 have noted transient cardiac dilatation in some patients with this infection.[18] In a review of chest radiography in Jamaican patients with leptospirosis, Lee and coworkers found that 4 of 44 patients (9%) had cardiomegaly.[19] Two of these four patients were thought to have had biventricular enlargement, while the other two had left ventricular enlargement only. On follow-up examination, three of the four patients had their hearts return to normal size, but the fourth had a persistently enlarged heart. In a similar study of 80 patients with Weil's disease in which 8 had clinical evidence of cardiac involvement, 2 had both radiographic cardiomegaly and signs and symptoms of congestive heart failure.[1]

Radiographic evidence of cardiac enlargement can be misleading. Although not yet reported, leptospirosis-induced pericarditis with an associated effusion might also present as cardiomegaly. The case reported here is the first in which there was echocardiographic evidence of left ventricular dilatation with reduced systolic function and a pericardial effusion. This is the modality of choice in determining the cause of cardiomegaly associated with leptospirosis.

Another finding that has been reported is both the radiographic and clinical evidence of pulmonary edema. Both cardiogenic and noncardiogenic pulmonary edema have been described. Several studies with adequate supporting hemodynamic data have shown that the adult respiratory distress syndrome (ARDS) can occur in association with leptospirosis.[20-22] It is likely that increased vascular permeability with a leakage of protein and fluid out of the intravascular compartment is responsible for the ARDS seen in these patients, but neither a specific circulating toxin nor intrapulmonic spirochetes have yet been isolated from patients with leptospirosis.[23,24]

Cardiogenic pulmonary edema occurs more frequently than does ARDS in patients with leptospirosis. The severity of this may range from an asymptomatic radiographic finding to overt cardiogenic shock with acute pulmonary edema.[10,13] Several studies report radiographic evidence of cardiogenic pulmonary edema,[4,13,25] but it must be remembered that this is difficult to distinguish from ARDS or hemorrhagic pneumonitis by chest radiography alone. Hemodynamic data or echocardiographic evidence of left ventricular dysfunction is required to adequately distinguish between these disorders.

Pulmonary edema appears to be a more common finding in patients with oliguric renal failure.[4,25] Whether this reflects a cardiogenic cause or volume overload has not been identified. In this population, invasive hemodynamic monitoring with a pulmonary artery catheter may also be useful in distinguishing between these various pathophysiologic processes.

Pathologic Findings

Involvement of the heart is a common postmortem finding in those patients who die of leptospirosis. Autopsy studies have reported histologic evidence of myocarditis in 50% to 100% of those hearts studied following death from this infection.[5,6,26] Involvement may range from small areas of focal inflammation to diffuse inflammation with interstitial edema. The inflammatory component consists primarily of lymphocytes and plasma cells; leukocytes are usually seen only in small numbers.[6] These inflammatory infiltrates are most commonly detected in the atria, atrioventricular region, and the interventricular septum.[5] In addition, petechiae or larger areas of hemorrhage may be found in as many as 80% of patients, most conspicuously in the epicardium but also occasionally in the endocardium or myocardium.[6] In one study of 33 postmortem examinations, 8 hearts were involved to the extent that cardiac failure was thought to have contributed to the patients' demise.[26]

When myocarditis is present, inflammation of the conduction system almost always exists.[5,6] To date, no correlation between postmortem findings and antemortem rhythm disturbances has been attempted.

Aortitis, with marked infiltration of lymphocytes and plasma cells into the aortic adventitia, has been found in 58% of the autopsies in one study.[5] This inflammation occurs

chiefly about the vasa vasorum of the aortic adventitia, with extension into the outer media.[5,26] Acute coronary arteritis, affecting the main branches of the coronary arteries, is even more common. DeBrito and colleagues found this in 14 of the 20 autopsies (70%) they performed for fatal leptospirosis.[5] Despite substantial inflammation, actual thrombosis of the coronary arteries was rare.[5] They also found that the presence of coronary arteritis closely correlated with histologic evidence of interstitial myocarditis.[5]

Valvular involvement may also occur in leptospirosis.[5] Two cases of vegetative endocarditis due to *Leptospira icterohaemorrhagiae* have been found at autopsy, but this is clearly an exceedingly rare phenomenon.[27]

Despite the clinical diagnosis of pericarditis in numerous patients with leptospirosis, autopsies usually fail to find significant pericardial inflammation. Whether an underlying epicarditis has been responsible for the pericardial friction rubs heard in these patients remains unknown.

Conclusion

A wide variety of cardiac manifestations may be seen in patients with severe leptospirosis. The mortality of these patients, who usually have both jaundice and azotemia, has been reported to range from 15% to 40%.[23,28] Despite myocardial involvement, death is usually the result of either renal or hepatic dysfunction.[28] Regardless of this, patients with severe leptospirosis should be closely observed for the development of cardiac involvement. Echocardiography or invasive hemodynamic monitoring may be useful tools in the management of either cardiomegaly or diffuse pulmonary infiltrates. With the prompt initiation of intravenous penicillin therapy, which is effective even when begun late in the course of the disease, it is hoped that the high mortality seen in these patients can be significantly reduced.[29]

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Adrenal Ganglioneuroma-Pheochromocytoma Secreting Vasoactive Intestinal Polypeptide

LILIANA N. CONTRERAS, MD
DIANNE BUDD, MD
T. S. BENEDICT YEN, MD
CAROL THOMAS, MD
J. BLAKE TYRRELL, MD
San Francisco, California

THE RARE SYNDROME of watery diarrhea, hypokalemia, and achlorhydria (WDHA) is presumed to be due to hypersecretion of vasoactive intestinal polypeptide (VIP).[1] In adults, this syndrome is most commonly caused by hyperplasia, adenoma, or carcinoma of the pancreatic islet cells, but it may also occur in patients with bronchogenic carcinoma, medullary thyroid carcinoma, retroperitoneal histiocytoma, and pheochromocytoma.[2] In contrast, neurogenic tumors such as ganglioneuroma and neuroblastoma are its most common cause in children.[3]

In this report we describe the case of an adult with the WDHA syndrome who in addition had hypercalcemia, hypercalciuria, hypertension, and hyperglycemia. The lesion was located in the right adrenal gland by computed tomographic (CT) scan, and elevated catecholamine secretion was recorded. The cause was an adrenal ganglioneuroma-pheochromocytoma secreting VIP and catecholamines.

Report of a Case

The patient, a 61-year-old man, was referred for evaluation of renal calculi. When seen, however, his major symptoms were chronic watery diarrhea and episodes of flushing.

(Contreras LN, Budd D, Yen TSB, Thomas C, Tyrrell JB: Adrenal ganglioneuroma-pheochromocytoma secreting vasoactive intestinal polypeptide. West J Med 1991 Mar; 154:334-337)

From the Metabolic Research Unit, Departments of Medicine and Pathology, University of California, San Francisco, School of Medicine.

Reprint requests to Dianne Budd, MD, Metabolic Section, Veterans Administration Medical Center, 111-F, 4150 Clement St, San Francisco, CA 94121.

ABBREVIATIONS USED IN TEXT

APUD = amine precursor uptake and decarboxylation [system]
CT = computed tomography
VIP = vasoactive intestinal polypeptide
WDHA = watery diarrhea, hypokalemia, and achlorhydria [syndrome]

The patient had had recurrent calcium nephrolithiasis, mild hypertension, hyperglycemia, and severe hypokalemia requiring more than 100 mEq per day of replacement therapy. Episodes of watery diarrhea began 3½ years before he was seen, but there had been no weight loss, nausea, vomiting, abdominal pain, tenesmus, mucus, or melena. This patient's diarrhea was resistant to several antidiarrheal agents but moderately responsive to fasting. In addition, the patient had sporadic episodes of facial and upper neck flushing. The only abnormality elicited on physical examination was a mildly elevated blood pressure of 142/90 mm of mercury with the patient standing.

Routine laboratory tests revealed normal values for liver function tests, complete blood count, sodium, chloride, bicarbonate, and urea nitrogen. The serum creatinine level was slightly elevated at 124 μmol per liter (1.4 mg per dl), and a random plasma glucose level was 9.9 mmol per liter (178 mg per dl). Serum potassium levels were maintained within the normal range only with the administration of 100 to 200 mEq of potassium chloride a day. Evaluation of the diarrhea revealed a 24-hour stool weight of greater than 2,000 grams, and stool fat measurements on two occasions were 53 and 190 mmol per day (15 and 54 grams per 24 hours; normal <18 mmol [5 grams] per day). Stool potassium levels were markedly elevated at 130 and 150 mmol per liter with simultaneous urinary potassium levels of 12 and 40 mmol per day. Radiologic studies including upper and lower gastrointestinal tract series were normal, as was a rectosigmoidoscopy. Gastrin, glucagon, and calcitonin levels were within normal limits. When the results of these studies suggested the WDHA syndrome, a VIP level was assayed and found to be elevated at 106 pmol per liter (320 pg per ml; normal 14 to 21.5 pmol per liter [42 to 65 pg per ml]).*

A workup for the cause of the renal calculi revealed a mild intermittent elevation of serum calcium levels, from 2.54 to 2.59 mmol per liter (10.2 to 10.4 mg per dl; normal 2.22 to 2.52 mmol per liter [8.9 to 10.1 mg per dl]), persistent hypercalciuria (urinary calcium 8.7 mmol [350 mg] per day) and mild hyperoxaluria (490 μmol [44 mg] per day). Parathyroid hormone concentrations were 44 and 71 μl equivalent per ml (normal <40 μl equivalent per ml). In addition, the patient had hypophosphatemia (0.39 to 0.90 mmol per liter [1.2 to 2.8 mg per dl]) and an elevated alkaline phosphatase level.

Because a pancreatic source of VIP hypersecretion was suspected, a CT scan of the abdomen was taken; it showed no abnormality of the pancreas, but a 5-cm right adrenal mass was identified. Further evaluation revealed that 24-hour values for urinary metanephrines and vanillylmandelic acid concentration were elevated at 9.3 μmol (1.7 mg) per day (normal <3.8 μmol [0.7 mg] per day) and 83 μmol (16.5 mg) per day (normal <50 μmol [10 mg] a day), respectively. In addition, a scintigraphic scan using iodine 131-labeled metaiodobenzylguanidine revealed increased isotope uptake in the right adrenal area.

Treatment with phenoxybenzamine hydrochloride, 20 mg twice a day, was started, and potassium chloride, 100 to 200 mEq per day, was continued. His blood pressure and serum potassium levels remained normal, but the diarrhea persisted. A month later, at abdominal exploration, a right adrenal tumor consistent with a pheochromocytoma was excised. During the operation a specimen of the right adrenal vein effluent was taken and found to have a VIP level of 264.8 pmol per liter (800 pg per ml). Extracts of the adrenal tumor tissue revealed a greatly elevated VIP concentration at 50 pg per mg of tissue.

The diarrhea ceased postoperatively, plasma VIP levels fell to 9.9 pmol per liter (30 pg per ml), and the patient's potassium level returned to normal without replacement therapy. A reevaluation of plasma catecholamine levels and urinary catecholamine metabolites showed normal values. Serum levels of parathyroid hormone, calcium, phosphorus, and magnesium were all normal after the adrenal tumor was resected.

Pathologic Description

The resected specimen was an adrenal gland measuring 3.5 by 2.5 by 2 cm with a cortical thickness of 0.2 cm that was attenuated at one end, at which point the medulla was contiguous with a tumor mass. The mass measured 5.9 by 5.5 by 4.5 cm and was encased in a bright yellow capsule. On sectioning, the tumor tissue was moderately firm with alternating areas of yellow and tan (Figure 1).

Histologically the tumor revealed two distinct patterns. Most areas sampled had a fibrous stroma with small and large nerve bundles. Embedded in the stroma were numerous large cells with granular cytoplasm and round nuclei containing prominent eosinophilic nucleoli resembling autonomic ganglion cells, a pattern consistent with ganglioneuroma (Figure 2, left). The rest of the tissue consisted of nests of smaller cells with varying amounts of cytoplasm, round to oval nuclei, and indistinct nucleoli, this being consistent with pheochromocytoma (Figure 2, right). Surrounding these

Figure 1.—The cut surface of adrenal tumor shows variegated yellow and red-brown areas.

*Plasma and tissue VIP assays were done by Sami I Said, MD, University of Illinois College of Medicine. Specificity data are from Said and Faloona.[1]

nests were interlacing capillaries. The two patterns merged with each other, although some distance from the border zones the patterns were distinct.

Special Studies

Unstained sections of the tumor were probed for the presence of VIP, calcitonin, and S-100 protein by the avidin-biotin-peroxidase complex technique.[4] Neither rabbit anti-calcitonin (Calbiochem) nor nonimmune rabbit serum showed staining (data not shown). Rabbit anti-S-100 serum (DAKO) strongly stained the Schwann cells in the ganglioneuroma element (Figure 3, left), as predicted from previous studies.[5] Rabbit anti-VIP serum (Calbiochem) strongly stained the cytoplasm of the ganglion cells, but there was only minimal cytoplasmic staining of the pheochromocytes (Figure 3, right).

Discussion

The production of peptide hormone is a property of cells derived from specialized ectoderm. The amine precursor uptake and decarboxylation (APUD) concept suggests that cells having the ability to produce peptide hormones are derived from a common neuroectodermal ancestry.[6] The APUD cells have two principal properties: they synthesize and store different types of amines, and they synthesize low-molecular-weight peptides.[7] Tumors arising directly from neural crest tissue offer a chance to explore ectopic hormone production.

In children, neurogenic tumors are common neoplasms of the posterior mediastinum and abdomen.[3] Ganglioneuromas have been reported in children in association with hypertension, diarrhea, or both. Because of the ability of neural crest tumors to secrete catecholamines, the pediatric literature previously ascribed an important role to these substances in the development of the diarrhea in patients with the watery diarrhea, hypokalemia, and achlorhydria syndrome.[8] With the availability of VIP assays and the elucidation of the properties of VIP, such as its role as a potent intestinal secretagogue, at least partially by the stimulation of adenylate cyclase, investigators suggested that this peptide's hypersecretion was involved in the cause of diarrhea.[9]

After Said and Mutt isolated VIP from porcine intes-

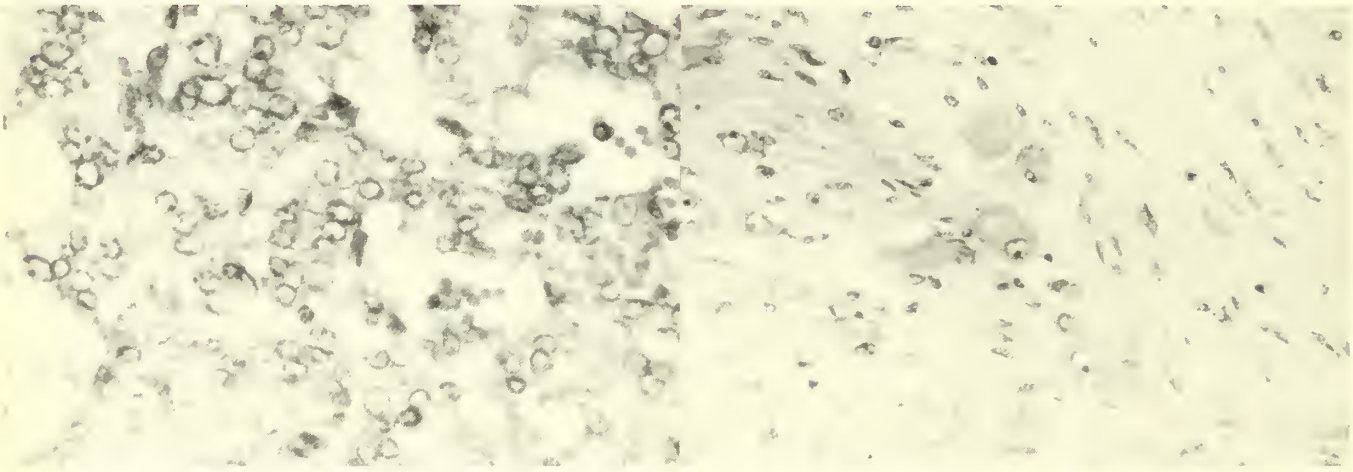

Figure 2.—Left, A micrograph of the ganglioneuroma portion of the tumor shows mature ganglion type cells, Schwann cells, and a fibrillary background (formaldehyde-fixed, paraffin-embedded tissue stained with hematoxylin-eosin [H&E]; original magnification × 400). **Right,** A micrograph of the pheochromocytoma portion shows typical cells in a "Zellballen" configuration with numerous capillaries (formaldehyde-fixed, paraffin-embedded tissue stained with H&E; original magnification × 400).

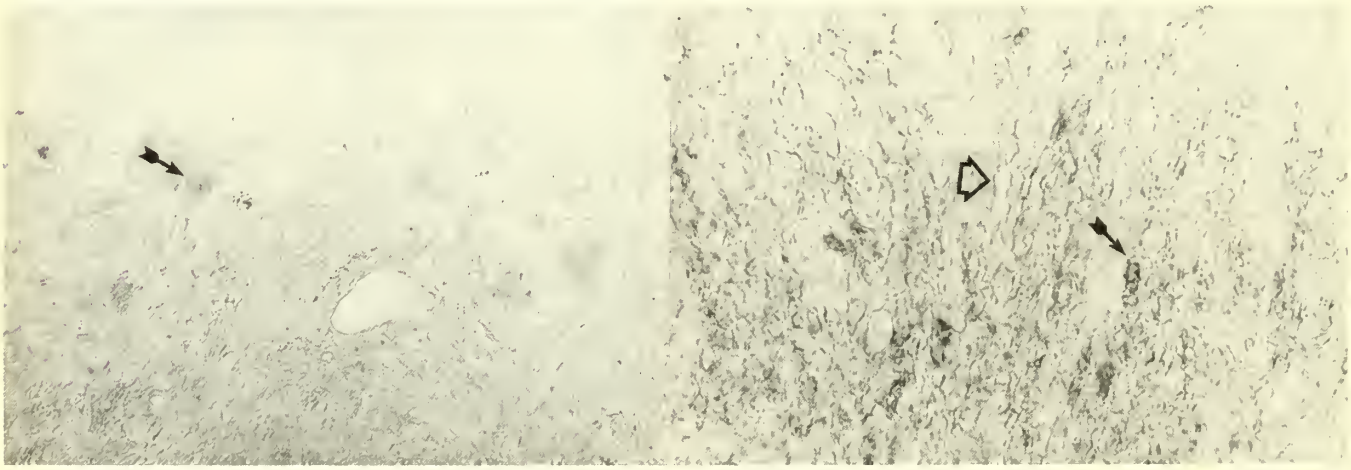

Figure 3.—Left, A micrograph of the ganglioneuroma portion of the tumor, after immunoperoxidase staining for vasoactive intestinal peptide, shows diffuse cytoplasmic staining of ganglion cells **(arrow)** (formaldehyde-fixed, paraffin-embedded tissue using avidin-biotin-peroxidase stain without counterstain; original magnification × 250). **Right,** A micrograph of the ganglioneuroma portion of the tumor, after immunoperoxidase staining for S-100 protein, shows nuclear staining of Schwann cells **(small arrow)** and staining of fibrils **(arrowhead)** (formaldehyde-fixed, paraffin-embedded tissue using avidin-biotin-peroxidase stain without counterstain; original magnification × 400).

tine,[10] high levels of this peptide were demonstrable in both serum and tumor tissue from children with the Verner-Morrison (or WDHA) syndrome. In these patients, the presence of mature forms of neural crest tumors and normal or increased catecholamine excretion was also documented.[11,12]

In adults, chronic watery diarrhea often complicated by hypokalemia and achlorhydria is frequently associated with pancreatic islet cell tumors.[13] Various nonpancreatic tumors, however, including pheochromocytoma, ganglioneuroblastoma, medullary thyroid carcinoma, and bronchogenic carcinoma have been described in association with the WDHA syndrome and elevated circulating plasma VIP levels.[1,2] The finding of two different histologic cell types in a single neoplasm of neuroectodermal origin was not described until Trump and co-workers reported the association of pheochromocytes and ganglion cells in an adrenal tumor of an adult with the WDHA syndrome.[14] Then in 1981 Choutet and associates reported finding both histologic types in an adrenal tumor incidentally found at laparotomy in a patient with hypertension and a family history of neurofibromatosis but no evidence of secretory diarrhea.[15] Recently a case has been reported of an adult patient with a pheochromocytoma-ganglioneuroma associated with the hypersecretion of VIP and secretory diarrhea.[16]

We describe the WDHA syndrome in a man with an adrenal ganglioneuroma-pheochromocytoma associated with high plasma and tumor tissue levels of VIP. Plasma VIP levels decreased with the concomitant cessation of diarrhea after surgical resection of the tumor. High vanillylmandelic acid and metanephrine levels were detected in this patient in association with mild hypertension. In previously described cases of WDHA found to be associated with pheochromocytomas, patients were not hypertensive.[14,16,17-21] This finding has been attributed to factors such as the dehydration resulting from severe diarrheal disease or the hypotensive effect of VIP. Unfortunately, in several of these patients catecholamine levels were not measured preoperatively. When elevated catecholamine levels have been recorded, the patients have been noted to have normal or low blood pressures. This case represents the first report of this disorder occurring in a hypertensive patient. After the resection of the adrenal tumor, vanillylmandelic acid and metanephrine excretion fell into the normal range; simultaneously, normal blood pressure levels were registered.

Intermittently high parathyroid hormone measurements and mildly elevated serum and urinary calcium levels were recorded during the course of the disease. After the operation, parathyroid hormone and serum calcium levels became normal, but urinary calcium excretion continued to fluctuate above the normal range. These mild elevations in serum and urinary calcium levels may have been related to the osteolytic activity of VIP,[9] although the persistence of urinary calcium variations after surgical therapy could have also been consistent with idiopathic hypercalciuria.

Normal gastrin, calcitonin, and glucagon levels were detected before the operation. These peptides and other substances including secretin, prostaglandins, pentagastrin, and gastrin inhibitory peptide have been postulated to be possible pathogenic factors leading to the clinical manifestations of pancreatic cholera.[12]

The findings in this case support the observation that tumors arising from neuroectodermal tissue have the ability to produce physiologically important peptides. The immunohistochemical studies done confirmed the production of VIP by ganglion cells. In contrast, the pheochromocytes did not stain for VIP. This finding agrees with the previous observations of Mendelsohn and colleagues who reported the presence of VIP in isolated ganglion cells of two pheochromocytomas whereas pheochromocytes and undifferentiated neuroblastic cells failed to stain for this peptide.[22] Nigawara and co-workers later reported similar findings.[21] Other investigators, however, have found VIP staining in both pheochromocytes and ganglionic cells.[20,23]

The detection of an elevated plasma VIP level may indicate the presence of neurogenic neoplasia. If catecholamine excretion is found to be elevated in a patient with the WDHA syndrome, the presence of an extrapancreatic tumor must be sought. Furthermore, its detection suggests that an underlying pheochromocytoma may be associated with other cells of neural crest origin responsible for the elevated circulating VIP levels.

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Thiazide Therapy and Severe Hypercalcemia in a Patient With Hyperparathyroidism

PHILIP STRONG, MD
San Diego, California

SARAH JEWELL, MD
JORDAN RINKER, MD
DANA HOCH, MD
LAWRENCE CRAPO, MD
San Jose, California

THIAZIDE DIURETICS can precipitate hypercalcemia in patients predisposed to this condition, such as those with primary hyperparathyroidism,[1,2] and can transiently elevate serum calcium levels in normal subjects.[3] Mild to moderate hypercalcemia has developed in patients receiving this type of medication. We describe the case of a patient who presented with severe hypercalcemia, electrocardiographic changes suggesting acute myocardial ischemia, and renal insufficiency following the institution of antihypertensive therapy with a combination of hydrochlorothiazide and triamterene. Symptomatically, the patient had a remarkable tolerance for severe hypercalcemia. In other respects, the case illustrates the typical manifestations of hypercalcemia involving multiple organ systems.

Report of a Case

The patient, a 61-year-old Iranian man, was brought to the emergency department by his family because of an inability to walk and was found to have a serum calcium level of 4.52 mmol per liter (18.1 mg per dl). Four months before admission, the patient immigrated to the United States. During a screening examination, he was told that he had hypertension and a large heart, and a regimen of methyldopa and digoxin was started. At a refugee health clinic ten weeks before admission, his calcium level was noted to be 2.69 mmol per liter (10.8 mg per dl), and he was referred to the hospital outpatient department for further evaluation. He was seen six weeks before admission, still hypertensive. The methyldopa dosage was increased, and the digoxin therapy was discontinued. Serum chemistry tests at that time revealed a calcium level of 2.72 mmol per liter (10.9 mg per dl), phosphate 0.45 mmol per liter (1.4 mg per dl), urea nitrogen 4.64 mmol per liter (13 mg per dl), and creatinine 106 μmol per liter (1.2 mg per dl). The patient was seen by a different provider 10 days before admission, at which time his medical records could not be located. The methyldopa therapy was discontinued, and a regimen of hydrochlorothiazide-triamterene (25 mg of hydrochlorothiazide and 50 mg of triamterene per day) was started. The patient became increasingly weak and, according to his family, somewhat confused. He began to have pain in the knees and ankles during this period.

On the day of admission, the patient's joint pain was severe enough to interfere with ambulation. In the emergency department, he complained only of constipation. His serum calcium level, as mentioned, was 4.52 mmol per liter, with a phosphate level of 1.42 mmol per liter (4.4 mg per dl). Hematologic studies showed a hemoglobin of 10.7 mmol per liter (17.2 grams per dl), hematocrit of 0.52, and a leukocyte count of 10.6×10^9 per liter. Serum chemistry tests showed a sodium level of 131 mmol per liter, potassium 3.2 mmol per liter, chloride 88 mmol per liter, bicarbonate 24 mmol per liter, urea nitrogen 22.1 mmol per liter (62 mg per dl), creatinine 336 μmol per liter (3.8 mg per dl), and glucose 11.8 mmol per liter (213 mg per dl). The uric acid level was 363 μmol per liter (6.1 mg per dl). Urinalysis showed a specific gravity of 1.010, a pH of 5, 1+ protein but no glucose or ketones, and no bacteria or cellular elements. The chest x-ray film showed a calcified nodule in the upper lobe of the left lung versus a calcified end of rib. The electrocardiogram (Figure 1-A) showed a mild sinus tachycardia with first-degree atrioventricular block, a QT interval that was short for the rate, and an early peaking T wave mimicking ST-segment elevation in leads V_2 through V_5.

The patient was admitted to the medical intensive care unit and started on a program of vigorous intravenous hydration and furosemide, together with etidronate, 1,600 mg orally per day for three days. The combination diuretic agent was stopped, and the patient's hypertension was controlled with nifedipine. After an initial rise to 5.06 mmol per liter (20.3 mg per dl), his calcium level fell to 3.64 mmol per liter (14.6 mg per dl) over the next three days. There was no initial improvement in his renal function. The electrocardiogram (Figure 1-B) continued to show a short QT interval with lessening of the ST-segment elevation. There was no enzymatic evidence for a myocardial infarction.

Plain abdominal x-ray films showed normal-sized kidneys and no abnormal calcifications. He subsequently had a normal abdominal computed tomographic (CT) scan. A chest CT scan showed minimal scarring in the left upper lobe of the lung with no abnormal calcifications, no mediastinal widening, and no hilar adenopathy. Skin tests for tuberculosis and coccidioidomycosis were negative with positive controls. A bone scan showed increased uptake in both knees and ankles consistent with osteoarthritis; in addition, a broad band of increased uptake with indistinct borders was noted in the occipitoparietal region of the skull. Skull films were normal. The results of serum and urine protein electrophoresis studies were normal. Thyroid function test values were normal.

On the fourth hospital day, the patient was given plicamycin (previously called mithramycin), 25 μg per kg of body weight by vein over eight hours. The serum calcium level decreased to 2.7 mmol per liter (10.8 mg per dl) the following morning. Over the next four days, the calcium concentrations varied between 2.74 and 3.02 mmol per liter (11 and 12.1 mg per dl) while the patient was placed on a regimen of oral hydration and furosemide. The phosphate value remained within the normal range. There was modest improvement in renal function. Pain in the knees and ankles worsened and interfered with ambulation; pain, swelling, and decreased range of motion of the wrists began on the seventh hospital day. Knee and ankle films showed chondrocalcino-

(Strong P, Jewell S, Rinker J, Hoch D, Crapo L: Thiazide therapy and severe hypercalcemia in a patient with hyperparathyroidism. West J Med 1991 Mar; 154:338-340)

From the Department of Medicine, University of California, San Diego, School of Medicine (Dr Strong), and the Department of Medicine, Santa Clara Valley Medical Center, San Jose, California (Drs Jewell, Rinker, Hoch, and Crapo).

Reprint requests to Lawrence Crapo, MD, Department of Medicine, Santa Clara Valley Medical Center, 751 S Bascom Ave, San Jose, CA 95128.

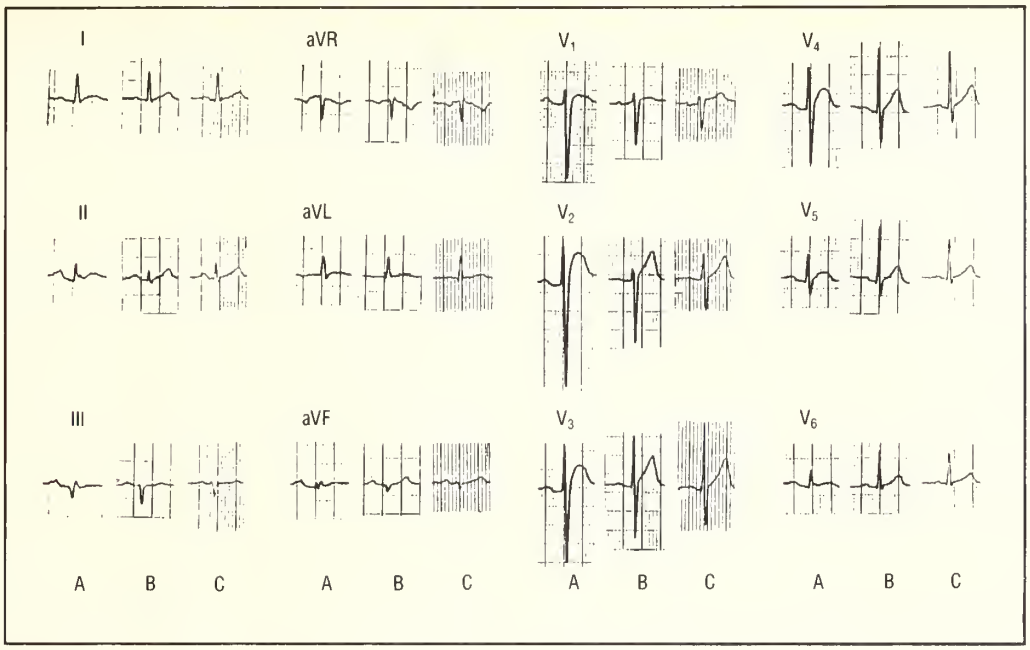

Figure 1.—**A,** The strips are from an electrocardiogram (ECG) taken on admission, when a serum calcium level was 4.52 mmol per liter (18.1 mg per dl). **B,** The ECG was taken 6 days later, when the calcium level was 2.6 mmol per liter (10.6 mg per dl). **C,** Four months after admission, the patient had a normal calcium value.

Figure 2.—An axial T2-weighted (TE = 80, TR = 2,800) magnetic resonance image of the neck shows high signal emanating from a large parathyroid adenoma (arrows).

sis, and there were small bilateral knee effusions. Wrist films were normal. A small amount of fluid removed from the left knee revealed minimal inflammation and no crystals.

On the tenth hospital day, the parathyroid hormone level, determined by immunoradiometric assay, was reported to be 1,040 ng per dl (upper limit of normal <65). The surgery service was consulted. Preoperative magnetic resonance imaging of the neck revealed a 2-cm mass adjacent to the thyroid gland consistent with a parathyroid lesion (Figure 2). At the operation, a 2- by 3-cm parathyroid adenoma was removed. After the operation, the patient's calcium level remained within the normal range; renal function steadily improved, with a serum creatinine level of 177 μmol per liter (2 mg per dl) before discharge; ambulation became less painful. The patient was discharged on the 18th hospital day.

Discussion

The three most common causes of hypercalcemia are hyperparathyroidism, accounting for 70% of cases in asymptomatic outpatients[4] and perhaps 20% of inpatient cases[5]; tumors, accounting for approximately 50% of inpatient cases[5]; and vitamin D-mediated conditions, such as hypervitaminosis D and sarcoidosis. Less common causes, accounting for fewer than 25% of cases, include other granulomatous diseases, immobilization, thyrotoxicosis, the milk-alkali syndrome, Addison's disease, vitamin A intoxication, the acquired immunodeficiency syndrome, Paget's disease, parenteral nutrition, rhabdomyolysis, and drug use—most notably thiazides, but also lithium,[6] theophylline,[7] and aspirin.[8]

Thiazides are thought to cause persistent hypercalcemia only in the presence of certain underlying conditions. Thiazide therapy for more than a few weeks' duration enhances distal tubular calcium reabsorption in the kidney, which results in hypocalciuria. In normal subjects, able to respond with appropriate, effective decreases in parathyroid hormone secretion, at most a transient mild increase in serum calcium levels can be observed. In patients for whom increased urinary calcium excretion plays a more important role in calcium homeostasis, persistent hypercalcemia can occur. It has been suggested that immobilization, Paget's disease, high-dose vitamin D therapy, and hyperparathyroidism can predispose patients to thiazide-induced hypercalcemia in this way.[9] Of these, only hyperparathyroidism has been clearly documented to have this effect.[10] In previously reported cases, mild to moderate hypercalcemia (2.7 to 3.5 mmol per liter [11 to 14 mg per dl]) was observed.

While the patient in this report was known to be taking a thiazide-containing diuretic, the nature of the predisposing condition was not initially clear. On admission, the normal serum phosphate value, the markedly elevated serum calcium level, the (questionable) left upper lobe nodule on a chest film, and the mild proteinuria seemed most suggestive of malignancy. The low phosphate level a month before

admission, however, was a major clue to the diagnosis of hyperparathyroidism, confirmed during the subsequent evaluation.

Severe hypercalcemia can cause electrocardiographic abnormalities. Arrhythmias and QT interval shortening are typical. There is another report of a patient who had extreme hypercalcemia—serum calcium level of 21.8 mg per dl—with ST-segment elevations in the precordial leads as seen in the present case.[11] The mechanism of this effect is unknown.

This is the most severe case of thiazide-induced hypercalcemia that we have seen reported. Shortly after admission, the patient had a strikingly elevated parathyroid hormone level. We speculate that before the thiazide therapy was instituted, the patient was near the limit of his ability to compensate for his extreme parathyroid autonomy, and the diuretic precipitated a dramatic decompensation. Other factors probably contributed to this patient's pronounced hypercalcemia, however.

Studies in animals have shown that potassium-sparing diuretics (including triamterene) decrease the ratio of calcium to sodium clearance in the kidney.[12] Amiloride, in particular, has an effect that is additive to that of chlorothiazide (suggesting an independent mechanism of action). This patient was taking a combination hydrochlorothiazide-triamterene diuretic. While we know of no studies that specifically show an additive effect of triamterene or that document a clinically important effect of potassium-sparing diuretics on calcium in humans, this may have contributed to the marked hypercalcemia noted here.

The relationship between serum calcium levels and the kidneys is complex. Hypercalcemia can impair renal function by several mechanisms.[13,14] Calcium is thought to have a direct vasoconstrictive effect on renal vasculature capable of reducing the glomerular filtration rate. Calcium has been shown to alter electrical forces in the renal ultrafiltration barrier, also contributing to a decreased glomerular filtration rate. Calcium inhibits the sodium-potassium adenosine triphosphatase level in the distal renal tubules, which can cause decreased active salt resorption and volume depletion. It also reduces renal cyclic adenosine monophosphate activity, which can cause decreased antidiuretic hormone activity and nephrogenic diabetes insipidus. Conversely, extracellular volume depletion aggravates hypercalcemia. The resulting increased renal avidity for sodium is thought to increase calcium reabsorption in the proximal renal tubules.[15] While we know of no studies specifically documenting this effect, the potential exists for a vicious cycle that may also have contributed to the pronounced hypercalcemia in this case.

In conclusion, this patient had a preexisting parathyroid adenoma and mild hypercalcemia and received combination antihypertensive therapy with hydrochlorothiazide-triamterene. After several weeks, severe hypercalcemia developed that required intensive management. This illustrates the possible danger that thiazide therapy poses to patients with hyperparathyroidism and possibly several other hypercalcemic conditions. It suggests that screening patients for hypercalcemia before initiating thiazide treatment may be indicated.

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Commentary

Human Health and Environmental Health

EDGAR WAYBURN, MD, *San Francisco, California*

From a talk given April 20, 1990, at the Pacific Presbyterian Medical Center, San Francisco, California

Physicians must get involved more deeply and more personally in combatting today's serious environmental problems. They need to recognize the health risks associated with continued environmental degradation. In medicine, if a promising drug proves to cause too severe side effects, its use is abandoned. As concerned humans, physicians must realize that human tinkering with the natural environment, regardless of the economic and material benefits, now threatens the healthy habitat of the human race. Let me describe the problems the world faces today.

We humans have not yet learned that everything on this earth we inhabit is interconnected, that every action we take has side effects, and that there's no such thing as a free lunch. The very improvements that we in our modern industrial society have made in the past 40 years have made us heedless and shuttered our eyes from dangerous reality. Consider our situation.

In the four short decades since 1950, the global economic product has nearly quintupled. On average, the global economic output of every decade since 1950 has matched the total economic output from the beginning of civilization to 1950. In these past four decades, the world's food crops have tripled, life expectancy has greatly increased, and both infant and child mortality have been reduced significantly. Many of the plagues of previous centuries have been conquered. Microscopic forms of life that threaten human life have been identified, and agents to destroy them have been developed. The art of surgery has been dramatically improved. Organ transplants now provide replacement for many worn-out or diseased human parts. Radiation, ultrasound, magnetic resonance, and even nuclear energy have become the tools of medicine.

Now, most of us in the industrial countries of the world live in incredible comfort, having at our disposal sophisticated energy systems, speedy transportation, the immediate exchange of information, an extraordinary choice of foods to eat, and the finest medical care the world has ever known. In fact, most of us live much better than did the royalty of a century ago, and the wealthy among us live more like gods.

So what's wrong?

In the same four decades that we came close to tripling our food crops, we lost nearly *one fifth* of the topsoil of our planet. In other words, in a very few years, we have paid for increased food production with precious topsoil that earth has been gathering for millions of years. We continue to lose topsoil at the rate of *24 billion tons* every year.

In these same four decades that our global economy quintupled, we have all but removed the old-growth trees in our temperate zone. In California alone, we have now reduced our virgin forests to just 5% of their original extent. Since 1950, we have also cut down a fifth of the tropical forests worldwide. As one side effect of this massive deforestation, we have lost an untold number of species of flora and fauna—in fact, tens of thousands of species—thus diminishing earth's biodiversity. As another side effect, we have significantly increased the carbon dioxide content of our air. We have also lost some 2% of the protective ozone layer in the upper atmosphere and far more than that in a hole over Antarctica, a hole that continues to grow in size every year. We may have seriously influenced our climate, as well, if global warming and bizarre weather patterns are any indication. (We know for a fact that global temperatures have increased by 0.6°C in the past 100 years, and computer models indicate that earth may be committed to a warming of another 1.5°C to 4.5°C in the next 40 years.)

We have been introducing increasing quantities of poisons and pollutants into the living space of our planet, into our air, our land, and our waters. Some of these poisons have been introduced deliberately—such as pesticides, herbicides, and other synthetic chemicals. In 1949 synthetic chemical production was practically new; between 1950 and 1985, however, the production of such chemicals as DDT and other pesticides, herbicides, food additives, industrial chemicals, plastics, and medical products increased almost tenfold, growing from an annual output of 24 billion pounds to an annual output of 225 billion pounds. The United States Toxic Substance Control Act lists more than 63,000 different chemical substances that have been used commercially in the United States in the past decade and a half—and new chemical substances are being introduced into this country at the rate of 1,500 per year. The worldwide production of chemical pesticides alone now comes to some *500 million pounds* a year. It is worth noting that only half of the insecticides now being produced ever reaches a crop and less than 1% ever reaches an insect.

There are numerous other poisons and pollutants that we have produced inadvertently, such as airborne wastes from industrial activities, ambient emissions from the combustion of fossil fuels, and chlorofluorocarbons that come from air

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Dr Wayburn, who is now retired from practice in internal medicine, is Senior Member at Large of the Editorial Board of THE WESTERN JOURNAL OF MEDICINE. He was president of the Sierra Club for five years (1961-1964, 1967-1969).

Reprint requests to Edgar Wayburn, MD, 314 30th Ave, San Francisco, CA 94141.

conditioning, refrigeration, and spray cans. In fact, we have made a gigantic sink out of the air we breathe, pouring into it increasingly large quantities of sulfur, carbon, nitrogen, methane, and heavy metals—the exhausts and by-products of our technological societies. The Environmental Protection Agency (EPA) estimates that industry alone released into the air in one recent year (1987) *2.7 billion tons* of hazardous pollutants. This figure does not include the billons of tons of air pollutants released into the air by automobiles, which, incidentally, have increased in number worldwide by 72 million vehicles since 1970.

The vast chemical potion with which we are flooding our atmosphere is transported by winds and air currents over long distances. As it travels, it undergoes various reactions as one chemical acts on another. Solar energy and moisture in the air also enter into the process. The result is the mass production in our air of dangerous chemical compounds such as sulfuric acid, carbon monoxide, nitric acids, low-level ozone, and chlorofluorocarbons. Washed onto the land in deadly acid rain, these pollutants enter our water systems as well.

In just the past three decades, we have doubled the quantity of our noxious garbage and other solid wastes. We in the United States are also producing hundreds of tons of hazardous waste, more toxic and nuclear waste than any other country in the world.

During the past four decades, earth's human population has more than doubled. We are presently crowding more than 5.5 billion souls into earth's limited living space, and we continue to add 95 million people a year. While the populations of the industrialized countries can now live like kings (the people of the United States consume a fifth of the earth's resources that are consumed globally every year), some 1.2 billion of earth's peoples now live in absolute poverty.

These are facts that are coming slowly to the attention of people all over the world. But why are they of particular concern to physicians? Why should we care if the last of the old-growth forests are leveled, if the production of synthetic chemicals is going on apace, or if something around a quarter of the world's population is living in absolute poverty? We should and must care because we care about people, and we are concerned with the healthy survival of people. As things now stand, far too many millions of people are suffering from environmentally caused disease and disability, and if we continue to insult our environment as we are now doing, we stand to damage earth's life-support system to the possible destruction of human survival.

Take the matter of the loss of stratospheric ozone, to which the removal of forests contributes substantially. Although ozone in the lower regions of earth's atmosphere can be dangerous to human health, ozone in the upper atmosphere absorbs harmful wavelengths of ultraviolet radiation from the sun and so shields all of life on the planet from its effects, which in humans are carcinogenic. The reduction of atmospheric ozone may not only cause radical climate changes, it may have serious health effects; according to a recent study, the risk of melanoma developing in Americans has increased dramatically in the past few decades—from 1 in 1,500 in 1935 to 1 in 120 today. A projected increase suggests that the risk of melanoma will rise to 1 in 90 by the end of the century if present trends continue. Similar increases in melanoma are reported around the world—significantly among black and other dark-skinned populations who were once thought to be immune.

Then there is the matter of air pollution, which everyone deplores for its obvious effects on some of the world's most famous monuments, from the Parthenon to the Taj Mahal, from Gettysburg to the Mayan ruins. Air pollution increasingly threatens food crops all over the earth: 10% of total crop losses in the world are attributed to air pollution. It is being increasingly documented that air pollution causes not only short-term breathing difficulties but long-term lung disease. Recent studies indicate that high levels of air pollution are damaging not only to people with asthma but to those with normal lungs. Breathing the air in Mexico City is equated to smoking two packs of cigarettes every day—80% of the children living in that city suffer from respiratory problems. The EPA reports that at least 125 million people in the United States breathe unhealthy air.

And why, aside from the sympathy it engenders, is it of critical concern to physicians that about a fourth of earth's peoples live in absolute poverty? The diseases attendant on poverty can be devastating: chronic diarrhea, chronic bronchitis (often caused by smoke from unventilated cook stoves), ascariasis, increased infant mortality because of poor (or lacking) prenatal care—the list goes on. And overlooking how many of these 1.2 billion desperately poor people are painfully hungry, at least 400 million of them—two thirds of whom are children—suffer from serious malnutrition. A third of these children are doomed to die before they reach the age of 5.

Added to this burgeoning human population is that the more populous countries are those where malnutrition is on the march. Life expectancy rates are decreasing in at least nine African countries where the birth rates are skyrocketing. Infant mortality rates are creeping up in such countries as Brazil, Ghana, and Mexico. In recent years, we have witnessed the death by starvation of literally millions of people. Today the food output per capita is decreasing in even the developed countries, and our future food production is subject to an increasingly capricious climate.

And what about synthetic chemicals? Unquestionably there are synthetic organic chemicals that play major roles in controlling disease and in making life easier for us. But the deleterious, even lethal, side effects of many synthetic chemicals are being increasingly recognized. For example, of the 70,000 synthetic chemicals presently in world trade, about half, or 35,000, are considered to be definitely or possibly harmful to human health by the Organization for Economic Cooperation and Development. Certain pesticides, specifically, are known to cause miscarriages, birth defects, and other reproductive anomalies. On a broader scale, the United Nations Environmental Program reports that in 1987 there were more than 100 million cases worldwide of pesticide poisoning. At another level, over 90% of the substances listed as possible human carcinogens by the US National Toxicity Program are synthetic organic chemicals. So are 110 of the 126 toxic compounds found on the priority list of the federal Clean Water Act.

Physicians need to care that the earth's forests are being removed, not just for aesthetic reasons, although these are valid, too, but for reasons of human well-being. We need to protect our Arctic National Wildlife Refuge and our offshore waters, again not only for aesthetic reasons, but to preserve

earth's biodiversity and a healthy environment. We need to work for clean air and clean water and the safe disposal of toxic wastes for the health of human communities as well as for our own personal comfort and safety. We need to recognize that not only the dignity but the health of humanity is threatened by massive world poverty. It is incumbent on us as physicians to recognize and address the environmental health problems, which are, after all, our particular concern.

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MEDICINE

The practice of medicine
Is not what it was
In my grandfather's time.

I remember him telling me
Of weeks that went by
When he would be paid
Only in chickens
Or only potatoes;

Of treating the families
Of striking miners
In Montrose or Telluride
Who could not pay at all;
Of delivering babies
(A total of twenty)
For a tribe of dirt farmers
Who paid one new-laid egg
Or a cup of spring water:

After sweating a breach birth
And twins at that,
At five in the morning
It was mighty good water.

When, fifty years later
He came back to the mountains
Middle-aged babies
Ran up in the street
Crying, Doc! Doc! eyes streaming,
Tried to kiss his old hands.

No, the practice of medicine
Is not what it was,
But it has its moments:

That morning in surgery
I regained consciousness
A little too early
And found the doctor
Kissing my hand,
Whispering, whispering,
It's all right, darling,
You're going to live.

for W.S., MD

CAROLYN KIZER
Sonoma, California

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Commentary

A Public Health Approach to Cholesterol
Confronting the 'TV-Auto-Supermarket Society'

THOMAS BODENHEIMER, MD, MPH, *San Francisco, California*

Coronary heart disease has been proved to be associated with a "high-risk" diet and with elevated blood cholesterol levels. The National Cholesterol Education Program has embarked on a campaign based on intensive medical treatment of 60 million Americans with high blood cholesterol levels, but the degree of benefit of dietary change or pharmaceutical intervention or both to reduce blood cholesterol values remains a subject of disagreement within the scientific community. Evidence from comparative international studies suggests that to lower coronary heart disease mortality substantially, dietary alterations and general societal changes must be greater than those possible under the National Cholesterol Education Program's approach of physician-centered patient counseling. The nation's priority to prevent coronary heart disease should be a public policy approach, the goal of which is to reduce for the entire population all coronary disease risk factors. In the dietary area, three proposals to reduce the availability of atherogenic foods are the use of warning labels on atherogenic foods, the prohibition of advertising for such high-risk foods, and the imposition of an excise tax on the same foods. We must confront the "TV-auto-supermarket society" that underlies our nation's high rate of coronary heart disease.

(Bodenheimer T: A public health approach to cholesterol—Confronting the 'TV-auto-supermarket society.' West J Med 1991 Mar; 154:344-348)

In recent years, Americans have become preoccupied with a previously obscure organic chemical: cholesterol. More than two thirds of American adults are aware that cholesterol is related to heart disease.[1] Behind this impressive display of public knowledge lie two critical scientific and public health questions: Does a rich diet (foods high in fat, saturated fat, cholesterol, and calories) correlate with increased serum cholesterol levels, which in turn are associated with coronary heart disease (CHD), and Does a reduction in fat, saturated fat, dietary cholesterol, and calories lead to a meaningful drop in serum cholesterol levels and a considerable reduction in the incidence of coronary heart disease and of overall mortality?

The answer to the first question is a definite yes. Although the etiology of coronary heart disease is multifactorial, almost no one disputes that the rich diet is a key contributor.[2] The second question presents greater difficulties and has become the focus of a major public health debate. The federal government, backed by many prestigious researchers, thinks that reducing serum cholesterol levels through dietary change or drug interventions or both can substantially reduce the CHD incidence.[3] But thoughtful skeptics have begun to express reservations.[4] Spurred by a widely read article in *Atlantic Monthly* (T. J. Moore, "The Cholesterol Myth," September 1989, pp 37-70), the media have begun to raise questions. At issue is a multibillion-dollar campaign against cholesterol led by the National Cholesterol Education Program (NCEP). Even more at issue are millions of Americans who may die of coronary heart disease over the next half century and beyond. Will the current response to the epidemic reduce the number of CHD deaths to the maximum possible extent given our current level of scientific understanding?

The answer is no. Our nation can do a better job of combating coronary heart disease and should initiate measures that approach the epidemic from a public health perspective. Although in this article I focus mainly on the atherogenic diet, I conclude by appealing for a broader public health agenda.

The Medicalization of Cholesterol

The NCEP, a project of the National Heart, Lung, and Blood Institute, has outlined two approaches to the problem of high serum cholesterol levels and CHD: a "patient-based approach that seeks to identify individuals at high risk who will benefit from intensive intervention efforts," and a public health strategy that "aims to shift the distribution of cholesterol levels in the entire population to a lower range."[3] Whether or not intended by the NCEP, most resources are being concentrated in the patient-based approach, a massive undertaking that defines a high proportion of Americans as candidates for cholesterol-lowering medical intervention.[5]

This mode of intervention could accurately be termed the "medicalization" of the diet-heart problem. "Medicalization" means that the problem is attacked by individual patients going to physicians who obtain laboratory measurements and prescribe diets or drugs to lower cholesterol levels. The alternative to a medicalized strategy is a public health campaign to eliminate the socioenvironmental factors that contribute to coronary heart disease. The chief route taken by the NCEP—the medicalized approach—involves all Americans 20 years of age and older visiting their physician at least every five years for a measurement of blood cholesterol. Persons with levels greater than 6.21 mmol per liter (240 mg per dl) require further tests of lipid profiles, the prescription of a diet for three months, and a stricter diet if

Dr Bodenheimer is an internist in private practice and Assistant Clinical Professor, University of California, San Francisco, School of Medicine.
Reprint requests to Thomas Bodenheimer, MD, 2517 San Bruno Ave, San Francisco, CA 94134.

ABBREVIATIONS USED IN TEXT

CHD = coronary heart disease
LDL = low-density lipoprotein
MRFIT = Multiple Risk Factor Intervention Trial
NCEP = National Cholesterol Education Program

follow-up laboratory testing does not show adequate lowering of low-density-lipoprotein (LDL) cholesterol levels. After three more months, cholesterol-lowering drug therapy is begun if the stricter diet fails. Persons with levels between 5.17 and 6.21 mmol per liter (200 and 240 mg per dl) who have two other CHD risk factors (one of which is male sex) are also placed in this intensive intervention group. Patients with cholesterol levels between 5.17 and 6.21 mmol per liter without other CHD risk factors are given diets and annual laboratory testing.[3] A total of 60 million Americans fall into the intensive intervention group.[5]

Critics of the NCEP approach focus on a key question: Even if the NCEP successfully brings 60 million Americans into the intensive intervention program, plus millions more into the less intensive diet-counseling program, will CHD mortality be substantially reduced and will life expectancy be increased? The studies are not conclusive. A total of seven early diet intervention studies produced equivocal results.[6] The large Multiple Risk Factor Intervention Trial (MRFIT), which intensively controlled the diet, smoking, and exercise of its participants, was able to reduce blood cholesterol levels by an average of only 6.7%.[7] Two widely quoted trials of drug treatment of elevated cholesterol levels—the Lipid Research Clinics Coronary Primary Prevention Trial and the Helsinki Heart Study—presented their findings in a manner that may have magnified the significance of the results. Furthermore, excess non-CHD mortality in the treated groups of these studies raises questions about the safety of cholesterol-lowering drugs.[4] Taylor and co-workers calculated the gain in life expectancy that would be achieved by lowering cholesterol levels by 6.7%, the mean reduction achieved by the MRFIT study. They found that for men aged 40 with cholesterol levels around 7.76 mmol per liter (300 mg per dl), cholesterol reduction would raise life expectancy by only seven months.[8] Oster and Epstein estimated that men between 35 and 39 years of age who start lifelong cholestyramine therapy for reducing cholesterol levels can expect to live seven months longer than those who do not take the drug; for men aged 55 to 59, the gain in life expectancy drops to six weeks.[9] Fries and colleagues argued that the major cholesterol intervention trials show no effect on total mortality.[10] In summary, although the link between CHD and cholesterol levels is indisputable, the benefit from therapy remains speculative.

Moreover, the NCEP approach is costly. Cholesterol-lowering cholestyramine therapy has been estimated to cost more than $2 million for each CHD death prevented.[11] Within five years, the annual sales of drugs to lower cholesterol levels will top $3.1 billion (S. Gannes, "Behind the Battle Over Cholesterol," *Fortune*, December 18, 1989, pp 101-116). Semiannual cholesterol testing for 60 million Americans at an average cost of $20 per person is $2.4 billion in laboratory work each year, not to mention several billion dollars more in physician visits. The total cost of implementing the NCEP recommendations may come to $10 to $20 billion per year (*Atlantic Monthly*, September 1989, pp 37-70).

Thus the NCEP patient-based approach to preventing CHD may be an expensive exercise of questionable benefit. Some critics imply that less—that is, less dieting, less drug treatment, less laboratory testing—rather than more should be done. Perhaps the critics have it backwards and our nation should do more, not less, to prevent CHD morbidity and mortality. But more of what?

Intervening More Aggressively

Studies of programs to alter rich diets show that individual dietary counseling is limited in its effectiveness. Counseling gains initial success in reducing dietary and serum lipid levels, but high rates of recidivism cause serum lipid levels to rise anew.[12]

Moreover, the amount of cholesterol lowering required to prevent coronary heart disease may be far greater than that advocated by the NCEP. The 1985 Consensus Conference on Lowering Blood Cholesterol to Prevent Heart Disease recommended that fat intake be reduced from 40% to 30% of calories and that adults be targeted for cholesterol levels of less than 5.17 mmol per liter (200 mg per dl). Yet in the traditional diet of Japan, where the rate of CHD is a tenth that in the United States,[13] fat makes up only 10% of calories.[14] Lipid researcher Basil Rifkind notes that "Plasma cholesterol concentrations above 150 mg per dl [3.88 mmol per liter] are unnecessarily high and put patients at risk for arterial deposition and its consequences."[15] In China, where CHD is rare, blood cholesterol levels of 4.65 mmol per liter (180 mg per dl) are considered high, with low levels ranging from 2.33 to 3.10 mmol per liter (90 to 120 mg per dl) (J. E. Brody, "Personal Health," *New York Times*, November 30, 1989, p B8). In contrast, the US mean cholesterol level is 5.51 mmol per liter (213 mg per dl).[2] Coronary heart disease is generally unknown as a public health problem in societies with mean cholesterol values of less than 3.88 mmol per liter (150 mg per dl).[16]

The data just reviewed present a clear message: the American population is massively hypercholesterolemic. A reasonable goal for the United States is a mean cholesterol level of 3.88 mmol per liter (150 mg per dl) or lower. To achieve such a goal, individual dietary counseling is likely to fail because of poor compliance, and drug therapy is of unproven long-term safety. To bring the mean US cholesterol level to a range of 3.88 mmol per liter or lower, we must look for interventions far beyond the medicalized approach of the NCEP.

Are We Winning or Losing?

Scientists working in the field of CHD prevention might make the following argument: Age-corrected CHD death rates fell an astonishing 42% between 1964 and 1985. An estimated 30% of this decline can be attributed to reductions in the nation's mean blood cholesterol level, which dropped about 0.18 mmol per liter (7 mg per dl) in the decade of the 1960s.[2,17] The intake of foods high in cholesterol and saturated fats has declined over the past 20 years.[18] It is clear that we are winning the war against coronary heart disease, and we should simply let current trends continue.

Such a hopeful prospect is not justified, however:

- Of the reduction in CHD mortality from 1968 to 1976,

40% can be attributed to improvements in medical care—coronary care units, prehospital resuscitation, coronary bypass surgery, and medical treatment of CHD and hypertension.[17] The positive effect of these interventions may have already reached its maximum.

- The consumption of tobacco declined by 29% from the early 1960s to the early 1980s,[13] and the rate of decrease has thus far not slowed down.[19] In the early 1980s, however, a million young people became new smokers each year, and the decline in smoking prevalence among high-school seniors has leveled off.[19,20] In addition, smoking prevalence among poorly educated persons has scarcely diminished.[21]

- Preliminary evidence shows that the rate of decline of CHD mortality may indeed be leveling off.[22] Around 1976, the rate of age-adjusted CHD decline slowed for white women and black men and women; white men did not experience such a slowdown. As a result of this slowdown, white and black women and black men suffered an estimated 40,000 more deaths from CHD in 1985 than would have occurred had the 1968 to 1975 trend continued.[23]

- Obesity is associated with increased blood cholesterol levels and is itself a long-term risk factor for coronary heart disease.[24] The prevalence of obesity is increasing among children and adolescents in the United States. Because childhood obesity often persists into adult life, the future population may experience more adult obesity, which could negatively affect cholesterol levels and CHD rates.[25,26]

- According to a 1987 *New York Times* survey, persons between 18 and 29 years of age have poorer eating habits than do older men and women and are more likely to eat high-fat foods (M. Burros, "What Americans Eat: Nutrition Can Wait, Survey Finds," January 6, 1988, pp 15-16).

- Although the per capita consumption of animal fats fell during the 1970s, it began to rise again during the early 1980s.[27] Cheese consumption has climbed from 13 lb per capita in 1972 to 24 lb in 1987.[28] Despite the nation's intense interest in diet and heart disease, total dietary fat as a percentage of calories has not changed substantially over the past 20 years, although saturated fat consumption has fallen.[22] Thus, overall dietary trends are not improving consistently, and the fast-food boom may create an atherosclerotic "McDonald's generation."

- The reduction in CHD mortality has been greater for the more educated than for the less educated.[18] Average serum cholesterol levels declined between 1960 and 1980 for whites but not for blacks.[29] Less-educated persons are more difficult to reach with preventive and curative interventions and will likely remain a reservoir of high CHD rates unless specially targeted programs are developed.

- Although the drop in CHD mortality is impressive, more than 500,000 Americans still die of this disease each year, with many deaths occurring in relatively young persons. The epidemic continues on a massive scale. Because the potential exists—as shown by rates in other nations—to substantially reduce CHD mortality, this illness merits the greatest possible public health efforts.

In summary, although we have registered major gains in the war on coronary heart disease, it is by no means clear that we are winning this war. Our nation needs strong public policy to lower CHD rates far beyond current levels. Evidence abounds that sufficiently large reductions in blood cholesterol values (beyond those achieved in most controlled trials) can have a major effect on CHD.[10]

Public Policy Options on High-Risk Foods

To substantially lower the mean cholesterol level of the US population requires a reduction in the availability of high-risk foods, such as those high in fat, saturated fat, cholesterol, and calories. Reducing the availability of these foods requires changes in the food industry, which makes such fare both available and attractive. The food industry has shown two contrasting trends in the 1980s. On the positive side, certain producers have responded to the consumer demand for less atherogenic foods. A number of companies have pledged to remove highly saturated tropical oils from their products. Lower fat dairy items allow consumers more choice than previously. Certain fast-food chains have reduced saturated fat use and have added such items as salads and baked potatoes. But the other trend, a disturbing one, has been the growth of high-fat fast-food sales. Between 40% and 55% of fast-food calories come from fat, a far higher percentage than the American Heart Association's recommendation of 30%.[30] From 1970 to 1980, fast-food sales grew 300% and in 1988 reached $61 billion (E. N. Berg, "Burger King's Big Comeback Bid," *New York Times*, October 29, 1989, p 4). Fast-food chains have expanded to elementary and secondary schools, colleges, military bases, and even hospitals. With the growing employment of women outside the home and the increasing number of persons living alone, these foods have become a permanent part of the American life-style.

An appropriate public policy would encourage food processors who engage in responsible behavior and would penalize those who continue to market high-risk foods. Three components of such a policy are warning labels on high-risk foods, the prohibition of advertising such foods, and the imposition of an excise tax.

Food Labeling

At present, the use of food labels is voluntary except on foods fortified with vitamins, minerals, or protein and on those with health-related claims on their packages. Except for foods packaged with claims of low cholesterol or low fat, there is no requirement that the cholesterol or fat content appear on the label.[31] During the late 1980s, a flurry of advertising appeared on packages heralding the low-fat, low-cholesterol, high-fiber, low-calorie attributes of foods ranging from breakfast cereals to chocolate ice cream. US Food and Drug Administration commissioner Frank Young acknowledged in 1989 that a number of these claims are misleading (P. J. Hilts, "FDA Criticizes Health Claims on Packages," *New York Times*, November 1, 1989, p A16), and the Bush administration announced plans in 1990 for stricter regulation of such advertising and mandatory nutritional labeling on most packaged foods (P. J. Hilts, "US Plans to Make Sweeping Changes in Labels on Food," *New York Times*, March 8, 1990, p 1).

But are these efforts adequate? Studies have shown that knowledge about nutrition has only a small influence on eating behavior.[26] According to the *New York Times* survey, many who claimed to watch their cholesterol at every meal were in fact consuming high-risk foods.

To be effective, labels must do more than simply list ingredients. The model for effective food labeling is the warning label required on cigarette packages and on alco-

holic beverages. Foods classified by the federal government as high in calories, cholesterol, and saturated fats—whether in supermarkets or fast-food establishments—could be required to display a label such as "The fat content of this food may contribute to heart disease."

Critics of such an approach argue that although no amount of cigarette smoking is beneficial, low levels of fat are essential nutrients. But a scientifically based classification scheme could ensure that only foods with high levels of atherogenic substances are given warning labels. The warning label approach is not unreasonable or farfetched. A *New York Times* editorial ("Foodbusters," February 2, 1990, p A18) suggested that fatty foods promoting heart disease be labeled with a "seal of disapproval." California's Proposition 65 requires that foods with carcinogens or reproductive toxins carry warning labels. Atherogenic foods also contain toxic products that contribute to many thousands of deaths. Just as an excess of vitamin A and vitamin D can produce toxic reactions, so it could be argued that an excess of saturated fat can be toxic. It is not illogical to view foods with excess fat content as toxic products that should be labeled as health hazards.

Banning the Advertising of High-Risk Foods

Public education has been an effective means of reducing the consumption of atherogenic foods; if people change what they demand, the food industry will change what it supplies. Public education can reduce the availability of unhealthy products; if Americans are taught that ice cream, steak, and French fries are killers, consumers will stop buying these items, profits on high-risk foods will fall, and the food industry will reinvest in frozen yogurt, broiled fish, and baked potatoes.

Such a strategy of altering consumer demand has its limits. Public confusion over which foods are healthy was as great in 1988 as it was in 1983, and nutrition education may not translate into improved food choices (N. Freundlich, "The Great American Health Pitch," *Business Week*, October 9, 1989, pp 114-133).[26] Two sectors of the population—the less educated and the young—are difficult to reach through public education and are highly susceptible to the message of the chief nutritional educators in our society: food companies and their advertising. The advertising budgets of food manufacturers will always far exceed governmental budgets dedicated to nutritional education. Regulatory reform of food advertising should therefore be a central component in preventing coronary heart disease.

The food industry spends $15 billion per year on advertising, 90% going to television commercials.[32] Food advertising on TV is specifically aimed at children; as many as 82% of ads on kids' programs feature food compared with 25% on adult TV; the average child sees between 15,000 and 20,000 commercials each year for edible items.[33] According to the Center for Science in the Public Interest, 80% of these commercials are for products with low nutritional value (written communication, July 11, 1989). McDonald's spends over $40 million each year on TV ads aimed at children (Standard and Poor, "Industry Surveys," July 4, 1985). A striking fact is that obesity among children aged 6 to 11 years has increased 54% in the past 20 years (Center for Science in the Public Interest).

The power of TV food ads cannot be ignored by advocates of CHD prevention. To succeed, public education must be combined with strict regulation of food advertising. Cigarette ads have been prohibited on radio and television, and a total ban on tobacco advertising is under discussion. A similar ban could be placed on the advertising of atherogenic foods; the same foods that receive warning labels could also be subject to the advertising ban. The "buckle up" campaign for automobile seat belts does not have to contend with TV celebrities persuasively discouraging seat belt use. The "just say no" campaign against illegal drugs does not compete with attractive video commercials promoting the use of such drugs. It is illogical to devote millions of dollars to nutritional education while billions are spent on harmful food ads.

Price Increases on High-Fat Foods

The antismoking movement has succeeded in raising the price of cigarettes through excise taxes. Studies have shown that high tobacco taxes do reduce consumption in all but the most heavily addicted.[34] Similarly, the prices of atherogenic foods could be raised through excise taxes. Such a tax could have its greatest effect on the hard-to-reach groups: lower income persons and children, who have the least money to spend. The same criteria used to denote foods as requiring warning labels and advertising bans could define foods taxable as atherogenic.

The 'TV-Auto-Supermarket Society'

Coronary heart disease prevention must reduce the availability of atherogenic foods but must also take a multifactorial approach. Diet is by no means the only social variable associated with high CHD mortality. In fact, dietary intervention to reduce cholesterol levels has less effect on life expectancy than does smoking cessation or blood pressure control.[8] If dollars per years of life saved is used as a measure, smoking cessation counseling goes farther than the treatment of hypercholesterolemia with cholestyramine therapy.[35] A sound public health approach must combat all CHD risk factors simultaneously.

Moreover, to battle CHD in a serious way means to address the larger societal question of why so many people eat rich foods, smoke cigarettes, lead sedentary lives, and endure the fast-paced, crowded, stressful emotional milieu of 20th (and probably 21st) century America. A proper examination of this question is the subject of a future article. In 1986 Stamler defined an entire societal complex related to the prevalence of CHD in the United States, the "TV-auto-supermarket society" (written communication, November 1986). This syndrome results in a gross caloric imbalance: processed foods from the supermarket containing high levels of fat and calories, a lack of physical activity created by the replacement of human muscle power with the automobile as the principal means of transport, and a further lack of activity produced by watching TV (which also implores us to buy cars and high-fat foods). To begin the search for a truly broad public health approach to coronary heart disease, we must confront the entire TV-auto-supermarket society.

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Editorials

Holding Our Heads High

THIS CENTURY has brought health miracles beyond our expectations. The typical American's life expectancy has increased by an average of more than two days each week since January 1, 1900. While much of this is due to a decrease in infant and child mortality, dramatic declines have occurred in death rates from heart disease and strokes. It is tempting to express our gratitude to medicine and science and look no deeper. But Dorothy Rice has looked deeper and presents a disturbing picture of a country that is not getting the best return on medical expenditures and, even more disturbing, a country that is less civilized in action than in rhetoric.[1]

The first step in reform is to get the facts. As George Washington wrote on March 15, 1793, regarding a statistical account of Scotland, "I am fully persuaded, that when enlightened men will take the trouble to examine so minutely into the state of society, as your inquiries seem to go, it must result in greatly ameliorating the condition of the people, promoting the interests of civil society, and the happiness of mankind at large."

Rice finds a variety of problems that plague our medical system. Two are of special import. First, we are not getting the desired effects from the money we spend. Despite the vast improvement in life expectancy, two of every three deaths in this country are still premature, given our skills and knowledge.[2] This is not due to inherent problems in medical care systems that have to be tolerated. The fact is that some countries extract more health results from their expenditures than we do. Granted, it is hard to agree on a single index of medical care systems. Infant mortality is often used as a measure of the medical care system, but it is actually a measure of the medical care and social systems combined. While every measure of medical care has some flaw, we are overwhelmed by the implications that a country such as Costa Rica has a life expectancy at birth of 75 years, an infant mortality rate below 20 per 1,000 live births, and a per capita gross national product of $1,690, a figure lower than our per capita expenditure just for health! Even Sri Lanka, with a gross national product of only $420, has been able to achieve a life expectancy at birth of 71 years.[3] These figures force us to raise serious questions about our stewardship of medical and health resources.

More troubling than waste or inefficiency is the lack of justice that becomes apparent when we consider inequities in access to medical care. It is a mockery to brag about the best medical system in the world if 35 million Americans are uninsured. How did this happen? The central battle of history has been between freedom and equality. Give people freedom, and soon a small percent are in control of the bulk of the wealth and power. Impose social equality, and one must curb individual freedom. The United States, in general, has balanced these two polar concepts as well as any society by starting with freedom and then collectively taking the fruits of freedom to provide a safety net for those unable to take full advantage of it. It is an attempt to provide equity, if not equality. Yet here we are, the richest and in some ways the most experienced society in balancing such concepts in history, looked up to and increasingly copied by others, and we haven't figured out how to make our medical expertise available to the poor.

We get tired of comparisons between our national spending on weapons versus that on social programs. And yet it is hard to find better measures of our priorities than how we allocate our resources. The prime medical-ethical battleground of our day is found in resource allocation, the seemingly dry analysis of budget line items. This cannot compete with the drama of court cases regarding the discontinuation of life support systems, but it more clearly reveals the soul of this nation. We find excuses to avoid investing in the medically uninsured while at the same time we find money for other things. The budget deficit is used to justify inaction on medical access for the poor while simultaneously the government finds unbelievably huge sums to bail out the savings and loan industry. As Rice reports, we even seem to be losing ground, with Medicaid covering only 45% of the poor when it once covered 60%.

Gandhi once said that his concept of the Golden Rule was that we must refuse to enjoy what is denied to millions. Most of us do not want to give up the benefits of a system that has offered so much to us personally. That gives us no option but to work for universal coverage of our entire population. This will not happen through voluntary systems. We need a collective solution, and that means a national government solution.

If, as a country, we cannot make our medical care system available to all, could we not agree to make it available at least to children and pregnant women? Rice points out that 11.3 million children under 18 years of age lack any form of insurance coverage. On September 30, 1990, 71 heads of state met at the United Nations building in New York to declare that the 1990s would provide a new ethic for the treatment of children of the world. Along with high level delegations from 69 other countries, these leaders set specific goals to be met by the year 2000. The goals are ambitious, calling for a 50% reduction in the incidence of severe malnutrition, deaths from diarrhea, and maternal mortality. The agreement calls for a 90% reduction in the 1.5 million deaths from measles each year, the elimination of polio and guinea worm, the provision of safe water supplies, and improved opportunities for education.

In short, the political leaders of this world committed themselves to change the way they will address the problems of children. Children will get the first call on resources, and national debts will not be paid at the expense of children's lives. The United States was part of this historic declaration.

There will always be a gap between what we could do and what we actually do. But there are also some irreducible minimums. That minimum must now include full access to medical care for the children of this country, not just to provide leadership in the 1990s, although it will do that, not just to hold our heads high, because it is still not enough, but because it is right if we are to "promote the interests of civil society, and the happiness of [humankind] . . ."

WILLIAM H. FOEGE, MD
Executive Director
The Carter Center of Emory University
Atlanta, Georgia

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Getting to Basics

HEALTH CARE for the poor, the young, the aging often means illness care. Even the very best care is not enough to help these most vulnerable, for they may be irretrievably sick before they receive attention. Illness care is necessary when safety nets, systems, and bodies break. We are faced with disturbing questions about this breakage.

- Why are "at least 4 million Americans (and possibly as many as 14 million) . . . now living on the knife edge of homelessness, already doubled-up with friends and family or one paycheck away from not being able to pay their rent?"[1]
- Even though $3 in short-term hospital costs are saved for every $1 spent on the prenatal portion of the Women, Infants, and Children Supplemental Food Program, why did only 59% of potentially eligible women and children receive this help in 1989?[2]
- Why do over 20 million Americans need drug and alcohol treatment?[3] Why is so little care available, especially for women, adolescents, and minorities?
- Why do African-American men in Harlem have a shorter life expectancy after age 40 than men in Bangladesh, with cardiovascular disease and cirrhosis the main causes of excess mortality?[4]
- Why are infant death rates in some parts of the United States higher than those in many Third World countries?
- Why is the number of Americans without any health care coverage increasing? Why is so little research undertaken in diseases of aging?

How did we get into the situation in which so much suffering occurs before health or illness care is received? Reasons seem plentiful. Federal spending for education training, employment, and human services has plummeted over $82.3 billion since 1982.[5] Military spending has grown. Bailouts and war have been undertaken. We are faced with conflicting, bewildering demands. We wallow in indecision. Private giving has not kept up with the need, nor can it. Brian O'Connell, president of Independent Sector, a national coalition of foundations, philanthropic corporations, and not-for-profit organizations, has noted that the voluntary sector has enormous vitality and provides crucial services but has limits. For example, nonprofit groups are able to spend about $250 billion per year compared to governmental spending of $2.5 trillion.[6]

Our national assets are plentiful. We have talent, money, natural resources, creativity. We can solve problems. We know what is right. We know that good food, homes, usable skills, and self-esteem will help the poor, the young, the aging. We know that failing to invest in these has led to unnecessary suffering for millions. Good health comes more easily to people who are well-nourished and well-clothed, to people who respect themselves. The basic issue is not health or illness care. The basic issue precedes the point at which this care must intervene. The basic issue is caring enough about the vulnerable to give them a hand. We do care, of course. We recognize the consequences of not investing in people. We must now pull together, clarify our values, reassert that vulnerable people are a high priority, and move ahead.

LINDA HAWES CLEVER, MD

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Meningeal Carcinomatosis

MENINGEAL CARCINOMATOSIS occurs when carcinomas, gliomas, sarcomas, melanomas, or lymphomas diffusely infiltrate the leptomeninges and subarachnoid space to produce a syndrome of chronic meningitis which may simulate that caused by fungi, tuberculosis, sarcoidosis, and meningovascular syphilis.[1,2] Although meningeal carcinomatosis was first reported with gastric carcinoma, today the more common tumors are usually responsible. In their series of 90 patients with meningeal carcinomatosis, Wasserstrom and co-workers reported that 46 patients had breast, 23 had lung, and 11 had melanoma primaries.[1] Evidence suggests that the incidence of meningeal carcinomatosis increases with longer survival.[3,4] Indeed, meningeal carcinomatosis primarily occurs late in the course of most patients' disease.

The pathogenesis of meningeal carcinomatosis is imperfectly understood. Recent data suggest that tumor enters the leptomeninges through several pathways, in part depending on the primary tumor type.[5] Lung and breast tumors most commonly invade from vertebral and paravertebral metastases; gastrointestinal cancer enters through perineural spaces. When deep central nervous system (CNS) parenchymal metastases are present, meningeal carcinomatosis follows cancer metastasis by the arterial route. The pathophysiology of clinical signs depends on local infiltration of the cortex, spinal cord, and cranial and spinal nerves. The usual regions of dense tumor growth are along the base of the brain and the dorsum of the spinal cord. Tumor growth along the base may obstruct cerebrospinal fluid (CSF) pathways leading to raised intracranial pressure and hydrocephalus. Experimental studies have elucidated some of the mechanisms responsible for the pathophysiology of the disease. In a model of B16 mouse melanoma-induced meningeal carcinomatosis, there was alteration of the blood-brain-CSF barrier, which allowed entry of the water-soluble drug, doxorubicin (Adriamycin).[6] In a rat model of meningeal carcinomatosis, the disease selectively lowered glucose use both in brain regions underlying the tumor and remote regions anatomically related to the former, helping to explain the diversity of neurologic dysfunction seen in patients.[7]

The clinical characteristics follow the pathogenesis; there is involvement of more than one CNS location—cerebral, cranial nerves, spinal cord, and spinal nerves. Common manifestations include headache, mental changes, cranial nerve palsies, weakness and areflexia, and minimal signs of meningeal irritation. Areflexia is common, as are urinary retention and other autonomic signs. The CSF findings generally establish the diagnosis. Pressure may be normal or elevated, the glucose content is often below 2.5 mmol per liter (45 mg per dl), the protein content is usually elevated, and cell counts may reveal an increased number of mononuclear cells or cytologic evidence of malignant cells, or both. The last occurs at some time in 90% of patients.[1] Cultures are negative. Carcinoembryonic antigen (CEA) and β-glucuronidase may be found in the CSF of patients harboring CNS

neoplasms, especially meningeal carcinomatosis.[8-10] Quantitative assay of the CSF for these markers may be useful in both the diagnosis and in following such patients. Another CSF marker, β_2-microglobulin, may be present in elevated levels in meningeal leukemia or lymphoma.[11] A computed tomographic (CT) scan may show hydrocephalus and contrast-enhanced subarachnoid or cortical nodules.[12,13] A gadolinium-enhanced magnetic resonance imaging (MRI) scan may show meningeal enhancement in as many as two thirds of patients; MRI is probably more sensitive than CT scan in detecting meningeal invasion.[14]

The treatment of meningeal carcinomatosis is difficult because the tumor involves the leptomeninges throughout the neuraxis. Theoretically, the best treatment of meningeal carcinomatosis would be irradiation of the entire neuraxis. Such a large radiation portal, however, includes the volume of bone marrow contained within the spine, and whole-neuraxis irradiation may prevent the patient from receiving a full dosage of systemic chemotherapy. For this reason, it is often elected to focus the radiation therapy to the area of clinically evident disease, usually the head or the lumbar spine, and then to treat the remaining meninges by chemotherapy.[1] Chemotherapy, using either methotrexate or cytarabine (cytosine arabinoside), is usually administered into the intrathecal space, either by lumbar puncture or by an Ommaya reservoir. The latter route assures drug entry into the ventricular and spinal subarachnoid spaces at therapeutic concentrations (for methotrexate, at least 1×10^{-6} mol per liter.)[15] Such treatment is often palliative. In the study of Wasserstrom and associates, 61% of breast cancer patients and 39% of lung cancer patients were improved or stabilized on this regimen.[1] The CSF findings frequently improved, opening pressures became normal, protein levels fell, glucose content returned to normal, and the cell count and cytology results frequently became normal. Melanoma patients fared poorly. Others have reported similar results with irradiation and methotrexate given by Ommaya reservoir.[16,17] Combination chemotherapy with methotrexate, cytarabine, hydrocortisone, and thiotepa delivered into the reservoirs has reportedly been effective.[18] Raised intracranial pressure, without or with hydrocephalus, may require ventriculosystemic (ventriculoperitoneal, ventriculoatrial) shunts. "On-off" valves are useful in the shunting systems because they permit the continuation of treatment with intra-Ommaya chemotherapy. The survival of patients with meningeal carcinomatosis is usually short—a median of 5.8 months in the study of Wasserstrom and colleagues[1]—although as with metastatic brain tumors, the systemic tumor is usually responsible for death.[1,19] Newer techniques of therapy may prove fruitful. In a pilot project, ^{131}I-labeled monoclonal antibodies have been administered intrathecally to five patients with leptomeningeal tumor with promising results.[20]

In the clinicopathologic conference so ably discussed by Mazziotta and colleagues, the patient had meningeal carcinomatosis from adenocarcinoma.[21] A primary tumor was not evident clinically, and thus the case lacked a most important clue to making the diagnosis. Even at autopsy the source of the tumor was not found, although the patient's long smoking history would favor a lung primary. The patient had many of the characteristics of meningeal carcinomatosis, including cortical involvement (seizure, mental deterioration), cranial nerve dysfunction, CSF pathway obstruction, and spinal nerve involvement. The CSF showed pleocytosis, an elevated protein level, and depressed glucose concentrations. The cytologic findings were negative, thus preventing a definitive diagnosis being made.

The case is clearly unusual, but this reviewer has several such cases in his practice. In the series of 90 patients reported by Wasserstrom and co-workers, there were 18 without evidence of systemic disease.[1] Of interest, many of these patients actually responded better and lived longer than those with systemic tumor. Given the difficult and potentially toxic treatment alternatives, meningeal biopsy can be highly recommended. Meningeal biopsy can be further justified if done as part of the procedure to place an Ommaya reservoir, as might have been considered in this patient.

Of the metastatic complications of tumor in the nervous system, meningeal carcinomatosis is the most difficult to treat. A number of studies have yielded important advances in treatment, however, and many patients can be successfully palliated, at least for awhile. The introduction of CSF marker analysis has made the diagnosis easier.

WILLIAM R. SHAPIRO, MD
Chair, Division of Neurology
Barrow Neurological Institute
St Joseph's Hospital and Medical Center
Phoenix, Arizona

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 500 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

An Easy and Inexpensive Way to Lower Cholesterol?

To THE EDITOR: After reading the article by Press and colleagues describing the cholesterol-lowering effects of the nutritional supplement chromium picolinate in the January 1990 issue,[1] I treated ten hypercholesterolemic patients with a regimen of chromium picolinate (200 μg chromium daily, a nutritional dose), niacin (1 to 2 grams per day, a pharmacologic dose), and dietary advice. After four weeks of this therapy, the average response was as follows:

- Total cholesterol levels dropped from 7.78 mmol per liter (301 mg per dl) to 5.92 mmol per liter (229 mg per dl) (24%).
- Low-density lipoprotein (LDL) cholesterol levels dropped from 5.66 mmol per liter (219 mg per dl) to 4.14 mmol per liter (160 mg per dl) (27%).
- Triglyceride levels dropped from 1.78 mmol per liter (158 mg per dl) to 1.02 mmol per liter (90 mg per dl) (43%).
- High-density lipoprotein (HDL) levels were unchanged at 1.32 mmol per liter (51 mg per dl); the ratio of LDL to HDL improved substantially, however.

Obviously, these anecdotal data do not allow us to judge the relative contribution of chromium alone to the success of this regimen; nevertheless, the response was certainly clinically notable and comparable to pharmacologic treatment with prescription medications. One patient was treated initially only with niacin; subsequent treatment with a lower dose of niacin plus chromium yielded a better response.

The treatment with chromium picolinate was convenient (one capsule daily), inexpensive, and was not associated with any discernible side effects. Patient acceptance was excellent.

Asymptomatic, insulin-resistant hyperinsulinemia is common in the Western world and appears to be an independent risk factor for cardiovascular disease.[2,3] By promoting tissue insulin sensitivity, good chromium nutrition may provide an additional protective benefit for many hypercholesterolemic persons.

We need controlled studies to assess the efficacy of chromium picolinate use alone, or as an adjunct to diet and niacin, in the treatment of hypercholesterolemia and hypertriglyceridemia.

JEOFFRY B. GORDON, MD
4747 Mission Blvd, Suite 4
San Diego, CA 92109

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Primary Biliary Cirrhosis Coexisting With Sarcoidosis—or Possibly Sjögren's Syndrome?

To THE EDITOR: Leff and colleagues recently reported the case of a 40-year-old woman with coexistence of primary biliary cirrhosis and sarcoidosis.[1] It is difficult to determine whether the pulmonary granulomas of this case were due to primary biliary cirrhosis or to coexistent sarcoidosis, however. Pulmonary manifestations in primary biliary cirrhosis can be attributed to the emergence of a granulomatous disorder in the lungs similar to sarcoidosis.[2] The patient had few symptoms or laboratory data that helped make the diagnosis of sarcoidosis. We agree that the case may represent the coexistence of primary biliary cirrhosis and sarcoidosis and, from the rheumatologic point of view, would like to make some comments.

Lymphocytic interstitial pneumonitis, or so-called pseudolymphoma, which is commonly associated with Sjögren's syndrome, may occur in patients with primary biliary cirrhosis, as Leff and co-workers mentioned in their article. Pseudolymphoma is most common in women in their 40s and often manifested as a tumorlike mass (coin lesion) in a chest radiograph. In these patients granulomas are sometimes observed.[3] Did this patient have any immunologic or histologic evidence of Sjögren's syndrome? Even if there were dry eyes and dry mouth, we must be circumspect in diagnosing sicca complex as Sjögren's syndrome because sarcoidosis has been associated with dry eyes and mouth.[4] Minor salivary gland biopsy is used also for diagnosing sarcoidosis, with results showing typical noncaseating granulomas in about half of patients.[4] We are intrigued with the possibility of the coexistence of sarcoidosis and Sjögren's syndrome.[5] An association of thyroiditis, Addison's disease, Sjögren's syndrome, and sarcoidosis—TASS syndrome—has also been reported from California.[6] It could be speculated that the histologic or clinical similarities among primary biliary cirrhosis, sarcoidosis, and Sjögren's syndrome suggest a continuum of disease.

HIDETO AKAMA, MD
Division of Rheumatology
Department of Internal Medicine
Keio University School of Medicine
35 Shinanomachi, Shinjuku-ku
Tokyo 160, Japan

TADASHI YOSHIDA, MD
SHINICHI KAWAI, MD
Division of Rheumatic Disease
Tokyo Metropolitan Ohtsuka Hospital
Tokyo 170, Japan

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* * *

Drs Leff and Schwarz Respond

To the Editor: Dr Akama and colleagues raise the interesting possibility that the patient we described as having coexistence of primary biliary cirrhosis and sarcoidosis[1] may have had instead Sjögren's syndrome complicated by lymphocytic interstitial pneumonitis (LIP) with pulmonary granulomas. It is clear that primary biliary cirrhosis is associated with Sjögren's syndrome, which is indeed associated with noncaseating granulomas on biopsy and which may be indistinguishable from those seen in sarcoidosis. For the following reasons, however, we think this is an unlikely scenario in our patient:

- The patient had no evidence of Sjögren's syndrome (although no salivary gland biopsies were done) or the sicca complex.
- There was no evidence on transbronchial lung biopsy of either LIP or pseudolymphoma to explain the pulmonary granulomas.
- Chest computed tomography showed no evidence of an interstitial process that might be expected in the case of LIP.

While we may have encountered a sampling error due to the bronchoscopic nature of the biopsies, we think the weight of the evidence suggests coexistent sarcoidosis.

JONATHAN A. LEFF, MD
MARVIN I. SCHWARZ, MD
Division of Pulmonary Sciences
University of Colorado Health Sciences Center
4200 E Ninth Ave
Denver, CO 80262

REFERENCE

1. Leff JA, Ready JB, Repetto C, Goff JS, Schwarz MI: Coexistence of primary biliary cirrhosis and sarcoidosis. West J Med 1990; 153:439-441

Transmission of Hepatitis B by a Surgeon

To the Editor: In 1987 Orange County Public Health learned of two acute cases of hepatitis B, and identified three additional reported cases from the previous two years, found by a review of public health records. All five persons had surgical procedures done by a surgeon who was a known hepatitis B carrier. The surgeon was found to have hepatitis B e antigen in the blood in addition to hepatitis B surface antigen. Furthermore, hepatitis B antigen was detected in sputum. Blood from three patients and the surgeon was available for typing of the surface antigen. All were type "ay." No other risk factors for hepatitis B were confirmed after careful histories were obtained from the patients. The surgeon's previous professional experience included doing multiple surgical procedures on persons at high risk of being hepatitis B carriers—dialysis patients.

None of the specific surgical procedures were known to have included any recorded incident of blood exposure or other untoward event. For this reason, the surgeon, hospital infection control committee representatives, and the local health department disease control director met and agreed that the surgeon should be required by action of the local health department to discontinue surgical practice and to observe appropriate precautions while doing minor procedures attendant to general medical practice. The decision was not contested and was thought to be in the best interests of the patients, the affected institutions, and the surgeon, since, unlike other reports of this nature,[1] no changes in practice or technique seemed likely to assure no further transmission. No further associated cases have been identified.

Orange County Public Health investigates all hepatitis reports (about 1,000 per year) using a procedure initiated by the Centers for Disease Control for use in "sentinel counties" engaged in a special study of hepatitis frequency and epidemiology.[2] Because the association of so many cases with a single physician does not occur commonly, it seems likely that some aspect of contact between the surgeon and patients resulted in transmission of the hepatitis B virus, even though no technical or procedural problems were identified. The surface antigen subtyping supports this conclusion but is not conclusive because the frequency of "ay" in the community is unknown.

Physician transmission of hepatitis B presumably is rare but may go unrecognized. We think it is important to record such recognized clusters so that representative accounts of such occurrences can be found in the literature.[3]

THOMAS J. PRENDERGAST, Jr, MD, MPH
Chief, Preventive Medical Services
San Bernardino County Department of Public Health
351 N Mountain View Ave, Rm 303
San Bernardino, CA 92415-0010

SOL TEITELBAUM, MD
Laboratory Director
Humana Hospital of West Anaheim
3033 W Orange Ave
Anaheim, CA 92805

BARBARA PECK, RN
Epidemiology and Disease Control Division
Orange County Public Health Department
PO Box 355
Santa Ana, CA 92702

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Correction

To the Editor: While the text is clear, Figure 1 in our case report on McCune-Albright syndrome in the December issue may be misleading.[1] Bromocriptine therapy was initiated in January 1985 before the decrement in prolactin values. We apologize for any confusion this may have caused readers of the journal.

ARTHUR L. M. SWISLOCKI, MD
University of California Service
VA Medical Center (612/111)
150 Muir Rd
Martinez, CA 94553

CARLOS A. CAMARGO, MD
ANDREW R. HOFFMAN, MD
Stanford University School of Medicine
VA Medical Center
3801 Miranda Ave
Palo Alto, CA 94304

REFERENCE

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Lessons From the Practice

The Patient's Wish

ERIC SCHNEIDER, MS, *San Francisco, California*

Our patient, Betsy Porter,* a 26-year-old mother of two boys, slept the serene sleep of anesthesia. The residents had neatly and swiftly opened her abdomen and exposed her uterus to our group in the operating theatre. Small and pale, the uterus was tightly bound down by fibrous tissue. It would not be freed quickly.

Weeks before, she had requested a hysterectomy to alleviate the intractable pain of endometriosis. From the beginning of her menstruating life, she had experienced increasingly disabling monthly pain. She wanted no more children. She had used a variety of licit and illicit drugs in the past—perhaps to combat her pain—but had, in her own words, "cleaned up her act." She was engaged to be remarried and seemed to have carefully planned her metamorphosis. We were to contribute to it. This operation was for her a clean break with her past—an opportunity to purge from herself not only the pain of endometriosis but also the other pains that had plagued her former life. Her fiance was agreeable. We, too, had agreed, at least to the extent that an operation could probably reduce the pain of endometriosis.

"Bring the ovaries into the field," the attending said. He was a deliberate and thoughtful man who always measured his words.

"According to the records, the left ovary was removed at Betsy's last operation," the chief resident commented, searching the fibrous scar. The right ovary came into view easily. It appeared remarkably normal—not at all responsible for the pain our patient had described. On the left, the dense scar tissue could not obscure a small piece of something dark.

"It appears that not all of the left ovary was removed at the previous surgery," the attending offered. "I would guess, from the way that ovarian remnant is encased in scar tissue, that it is the cause of this woman's pain. The right ovary looks perfectly normal. Perhaps we should consider leaving the right ovary tacked to the abdominal wall to give her an endogenous source of estrogens. Otherwise we commit her, at 26, to a lifetime of estrogen replacement therapy."

There was a silence as the chief resident turned the aberrant fragment of ovary slowly, trying to convince herself of what the attending had said.

She finally said, "In my discussions with Betsy, she was convinced of the potential role of the ovaries in producing the pain of endometriosis. She fully believes that the reason her last operation failed was that the right ovary was left in place. She was adamant about having it removed. She really wants to be rid of it."

The attending asked, "Do we do the surgery that to the best of our knowledge and experience will decrease this woman's pain and spare her the expense and complications of taking oral estrogens, or do we presume that the customer is always right and knows what is best?"

In medical school these days, there is much teaching about patients' right to make important choices concerning their care, about fully informing patients of the relevant facts, and about respecting patients' wishes.

The chief resident tried to be pragmatic: "If she wakes up with an ovary she will be very disappointed, and there is a high likelihood that she will continue to have pain. Then she'll go elsewhere to have the operation she wants. If we don't take everything now, she'll have a third operation, with the morbidity of that and, in the end, the estrogen replacement therapy." The chief resident was not entirely comfortable arguing for bilateral oophorectomy for a 26-year-old.

They decided to start by removing the uterus and the entrapped fragment of left ovary. I didn't know whether they were buying time to think about whether to spare the right ovary or whether this was the best approach given the dense fibrotic tissue on the left side.

It would have been ideal to wake the patient and explain the new situation, find out her opinion, and then proceed, but her only voice now was the steady wheezing of the respirator. The attending guided us through the anatomy as the operation proceeded. Fanning ligaments conveying living nerves and vessels rose up, were clamped and cut. The only sound was the metallic clanking of the surgical instruments handed back and forth in a steady rhythm. The scrub nurse sorted them. The anesthesiologist tended his machines. For a time, there was no patient. But before long, the right ovary presented its dilemma again. A clamp hovered over the ovarian artery. The operation ground to a halt. The operating room telephone rang. The circulating nurse picked it up.

"That ovary is terribly normal-looking," said the attending. It seemed to pulse like a small heart. With the uterus gone and the delicate fingers of the fallopian tube no longer stretched toward it, its remaining function was purely endocrine. If kept, it could for years release tiny amounts of estrogens to protect this woman against heart disease and osteoporosis.

Couldn't we somehow wake her long enough to explain the new situation, to show her with a mirror the harmless ovary, and to ask her then if she did not want it?

"Excuse me," called the circulating nurse, holding his hand over the telephone's mouthpiece. "Is there an Elizabeth Porter here?" There was a chill. The ovary gleamed under the brilliant lights. What operator had tried to put that call through?

The attending spoke softly for us all. "She's on the table. Can she call back?"

*The patient's name is fictitious.

(Schneider E: The patient's wish. West J Med 1991 Mar; 154:354)

The author is a fourth-year medical student at the University of California, San Francisco, School of Medicine.
Reprint requests to Eric Schneider, 1438 20th Ave, San Francisco, CA 94122.

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Am Fam Phys 1987;36:133-140

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• Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of **serum-sickness-like** reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
• Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
• Gastrointestinal (mostly diarrhea): 2.5%
• Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
• As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
• Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
• Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

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THE WESTERN JOURNAL OF MEDICINE
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PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

OB/GYN. BC/BE to join 20 physician (OB, Pediatrics, Internal Medicine) practice in sunny central Washington. Reasonable call schedule with three OB/GYN department. Loan repayment program available. Competitive salary, excellent benefit package including vacation at 30 days per year and professional liability. Contact Ann Garza, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

MARYSVILLE (YUBA COUNTY). Primary care provider. Northern California primary care clinic. Three physicians, three physician assistants. No OB. No surgery. Close to Sacramento, 2½ hours to Lake Tahoe and San Francisco. Salary $97,393.80. Send CV to Ed Allen, Peach Tree Clinic, 6000 Lindhurst, Ste 601-A, Marysville, CA 95901; or call (916) 741-6400.

LOOKING FOR A PRIMARY CARE Internal Medicine Geriatric position with challenging and appreciative patients, quality associates, tolerable schedules in an attractive community? Send CV to Julie A. Prazich, MD, Medical Director, Sharp Senior HealthCare, 3545 Fourth Ave, San Diego, CA 92103.

PHYSICIANS WANTED

PHYSICIAN OPPORTUNITIES NATIONWIDE

For all specialities for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

SAN FRANCISCO EAST BAY. BE/BC Internist needed to join ten physician Primary Care group practice in beautiful San Ramon Valley area. Excellent opportunity and compensation. Reply in confidence to Number 223, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE FAMILY PRACTITIONER to enjoy rural living with urban culture 20 minutes away. Generous vacation time to use the many nearby recreational opportunities. Join another Family Practitioner and two Physician Assistants in a Family Practice satellite of a large multispecialty clinic. Contact Jerry Corn, MD: (206) 687-5108 or Karen Stanton; (206) 254-1240.

SPOKANE, WASHINGTON. Primary Care Physicians join with Annashae Corporation in providing patient care to the families of the men and women serving in the Armed Forces, including those stationed in the Middle East. Immediate Emergency Room positions available in Spokane, Washington. Weekends and holidays. Competitive remuneration. Malpractice covered. Licensure any state. ACLS required. Contact in confidence Annashae Corporation, 230 Alpha Park, Cleveland, OH 44143-2202; 1 (800) 245-2662, EEC/MF. Support the troops, their families, and our country!

SOUTHERN CALIFORNIA

Upscale, family oriented community in the eastern foothills of Los Angeles County offers qualified primary care physicians (Family Practice, General Internist, Pediatricians) both group and private practice opportunities. Complete compensation package includes salary guarantees, practice management and marketing support, malpractice, and relocation expense reimbursement. BC/BE. Excellent growth potential. Send CV to Gary May, Foothill Presbyterian Hospital, 250 S. Grand Ave, Glendora, CA 91740; or call (B1B) 963-B411.

PHYSICIANS WANTED

PHYSICIANS NEEDED

The continuing growth of our service area population (now 90,000) has created an immediate need for additional 8C/8E physicians in the following specialities:

- **NEUROLOGY.** Establish private practice with no investment, guaranteed income. Proficiency in EEG, EMG required.
- **GENERAL/THORACIC SURGERY.** Establish private practice in General and Thoracic Surgery (no open heart) with no investment, guaranteed income.
- **ONCOLOGY.** Establish private practice with no investment, guaranteed income. Some General Internal Medicine necessary initially.
- **ORTHOPEDIC SURGERY.** No investment, guaranteed income. Above average earning potential.
- **RADIOLOGY.** Hospital group position. Excellent salary and benefit package. Competency in ultrasound, CAT, Nuclear Medicine, film screen mammography, and general diagnosis required. MRI experience desired. Inpatient and outpatient. (California license is required.)
- **PEDIATRICIAN.** Join busy private Pediatric Practice. Attractive salary with arrangements for future association.
- **FAMILY PHYSICIAN.** Join busy Family Practice group (four Family Practitioners) in private practice. Salary or guarantee first year.

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 90,000; a growing area with new businesses and a stable economy.

Located in central California near Sequoia National Park, Tulare offers an excellent family oriented lifestyle and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

Contact:

Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is searching for physicians residency trained or BC in Emergency Medicine. The Health Science Campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level One Trauma Center, has paramedic base station training responsibilities, and has a helicopter service. An approved Emergency Medicine Residency Program began in July 1990. Emergency Physicians supervise medical students, interns, and residents, in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive, and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

RADIOLOGIST—SAN FRANCISCO BAY AREA. Growing outpatient imaging practice with CT/MRI. Salary leading to partnership. Send CV to Murray Solomon, MD, 450 Sutter St, Ste 835, San Francisco, CA 94108; (415) 296-8654.

(Continued on Page 358)

PUT YOUR MEDICAL CAREER IN FLIGHT.

Discover the thrill of flying, the end of office overhead and the enjoyment of a general practice as an Air Force flight surgeon. Talk to an Air Force medical program manager about the tremendous benefits of being an Air Force medical officer:

- Quality lifestyle, quality practice
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1-800-423-USAF

AIR FORCE

(Continued from Page 356)

PHYSICIANS WANTED

OB/GYN, INTERNISTS, Family Practitioners, Pediatricians for Arizona and western opportunities. Quality positions available other regions of country. Inquiries confidential. Mitchell & Associates, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

RADIOLOGIST. Part-time position available immediately in small hospital with general Radiography and Fluoroscopy, Mammography, and Ultrasound in Weaverville, California. Contact Drs Wheeler, Biggs, or Babbitt, West Coast Radiology, 3798 Janes Rd, Ste 12, Arcata, CA 95521; office number (707) 822-3621, ext 191.

NORTHERN CALIFORNIA—INTERNAL MEDICINE. The Permanente Medical Group is seeking a BC/BE Internist to join their thriving practice located in Redwood City. Critical care experience helpful but not crucial. We offer a highly competitive salary and a substantial benefits package which includes malpractice insurance, medical, dental and group life insurance, educational leave, an excellent retirement program and a desirable San Francisco bay area location. Please respond with CV to Norman Olson, MD, Chief, Department of Medicine, 1150 Veterans Blvd, Redwood City, CA 94603. EOE.

TWO INTERNISTS seek an associate BE/BC Internist for busy Internal Medicine group practice located in a community of 60,000. Forty miles from San Francisco. Excellent modern hospital. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

A BE/BC NEPHROLOGIST is needed to join a two doctor practice in Nephrology forty miles from San Francisco. Excellent modern hospital with Chronic Dialysis unit next door. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

CHEYENNE, WYOMING. Immediate opening available for a dedicated, career oriented, full-time physician with Urgent Care facility in Cheyenne, Wyoming. Competitive compensation plus malpractice insurance. Approximately 14 days per month, standard 12 hour shifts. Excellent living conditions, high quality school system, moderate taxes and living expenses, exciting recreational opportunities in the heart of the Rocky Mountain region. Call now for additional information or send CV to Janet Cowley, Recruitment Coordinator, PO Box 805, Cheyenne, WY 82003; call toll-free, (800) 877-1436, or (307) 632-1436, FAX (307) 635-4642.

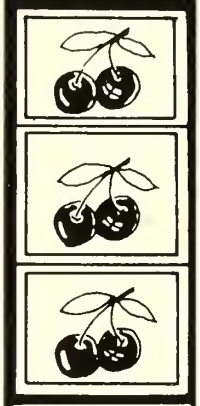
CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Room Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

SEATTLE: BC/BE General Internist to join BC Internists' group with three Seattle area offices. No income guarantee; group and location excellent. Call or write Douglas Bovee, MD, 3203 W. McGraw, Seattle, WA 98199; (206) 285-3139.

COASTAL CALIFORNIA 45,000 population. Well-trained 12 physician Primary Care group. Immediate/future need for Family Practice and Internal Medicine. Competitive salary and benefits with partnership after one year. On call schedule allows time for family and recreation. In Lompoc, you can do what you were trained to do, including OB, Pediatrics, and General Medicine. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

(Continued on Page 359)

ADS GET RESULTS



CLASSIFIED INFO (415) 882-3376

DON'T FORGET!

The deadline for submitting classifieds for the May issue of WJM is March 25.

Send your advertisement to:

Classified Advertising WJM, PO Box 7602 San Francisco, CA 94120-7602

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The benefits of group practice.

Physicians who want to enjoy the advantages of group practice without an administrative burden will really appreciate CIGNA Healthplan.

As a physician at one of CIGNA's health care centers, you'll join a team of equally dedicated physicians practicing within a consultative environment. But, unlike a group practice, your administrative work is carefully orchestrated by a competent staff of CIGNA Healthplan employees, enabling you to focus on patient care.

Currently, we have practice opportunities available for:

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Anesthesiologist	Neonatologist
Department Heads	Nephrologist
· Medicine	OB/GYN
· Oncology	Orthopedic Surgeons
Dermatologist	Otolaryngologist
Family Physician	Pathologist
General Internist	Pediatrician
Cardiologist	Pulmonologist

ARIZONA
Phoenix

Family Physicians	Orthopedic Surgeons
Internists	Pediatricians
OB/GYNs	Radiologists
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As one of the nation's oldest and largest managed health care companies, CIGNA Healthplan understands the environment and resources physicians need to practice quality care.

We offer a competitive compensation and benefits package, paid malpractice insurance and continuing medical education. To receive more information about becoming a CIGNA Healthplan physician, please call or send your CV to one of the addresses listed below:

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Glendale, CA 91203
800-468-9013

Arizona
CIGNA Healthplan
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Dept. 49
P.O. Box 16145
Phoenix, AZ 85011-6145
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CIGNA

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PHYSICIANS WANTED

FAMILY PRACTITIONER PEDIATRICIAN

Multispecialty group located in San Luis Obispo, California, seeks BC/BE physicians. Fringe benefits plus practice costs paid and shareholder status. Submit your CV to:

Physician Recruitment
San Luis Medical Clinic
1235 Osos St
San Luis Obispo, CA 93401

BOARD CERTIFIED FAMILY PHYSICIAN wanted to join two others within larger multispecialty practice in Kauai. OB preferred. Send CV to Drs Clay and Ratliff at 4366 Kukui Grove St, Ste 201, Lihue, HI 96766; or call (808) 245-4600.

CALIFORNIA. Immediate permanent placement opportunities in Internal Medicine, Plastic Surgery, Urgent Care, Pediatrics, Otolaryngology, Family Practice, and Dermatology. For information call or send CV to Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762; FAX (415) 376-0813.

PATHOLOGIST, BC/BE—CENTRAL CALIFORNIA VALLEY. Seven member group seeks associate for independent multiple hospital and private laboratory practice. Send CV to Robert F. Chard, MD, Delta Pathology Associates Medical Group, 2291 W. March Ln, Ste 179E, Stockton, CA 95207.

CHIEF, CLINICAL GERONTOLOGY SERVICE, Rancho Los Amigos Medical Center, Director—Section of Geriatrics, Department of Family Medicine, University of Southern California. Unique opportunity to direct a well established rehabilitation-oriented Geriatric Program in one of the largest rehabilitation facilities in the world. BC Family Physician with CAQ in Geriatrics will direct the clinical Gerontology service of Rancho Los Amigos Medical Center and serve as the director of our ACGME approved Geriatrics fellowship program. This will include a full-time faculty appointment as director, Division of Geriatrics, Department of Family Medicine at USC, at rank appropriate to individual qualifications. Rancho serves as a regional training site in Geriatrics for four Family Practice residencies, medical students, and allied health students. As one of two national Rehabilitation Research and Training Centers on Aging, many opportunities exist for participation in ongoing research projects, and development of personal research and regional and national training programs. Interested parties should contact Robert Waters, MD, Medical Director, Rancho Los Amigos Medical Center, Chairman, Search Committee, 7601 E. Imperial Highway, Downey, CA 90242, or Peter V. Lee, MD, Professor and Chairman, Department of Family Medicine, USC School of Medicine, 1420 San Pablo St, B205, Los Angeles, CA 90033; (213) 342-1313.

OBSTETRICS/GYNECOLOGY SOUTHERN CALIFORNIA: KAISER PERMANENTE

Join the nation's largest physician-managed, multispecialty medical group. We offer a choice of professional environments ranging from a 250-bed community hospital to a major teaching facility, highly competitive income, paid malpractice insurance, and much more. Send your CV to:

Irwin P. Goldstein, MD
Associate Medical Director
SOUTHERN CALIFORNIA MEDICAL GROUP
Dept 057
Walnut Center, Pasadena, CA 91188-8013;
or call: 1 (800) 541-7946

PHYSICIANS WANTED

Come Enjoy a Quality *Inland Northwest* Lifestyle in Spokane, Washington

Join this well established 80 physician owned and operated multispecialty group offering excellent practice opportunities to the BC/BE physicians in the following specialties:

CARDIOLOGY	OCCUPATIONAL MEDICINE
DERMATOLOGY	ORTHOPEDICS
FAMILY PRACTICE	PEDIATRICS
NEPHROLOGY	RHEUMATOLOGY

Attractive benefit package includes competitive salary leading to early shareholder status. High productivity is generously rewarded.

CONTACT: **Colleen Mooney, Recruitment Coordinator**

Rockwood Clinic, PS

E. 400 Fifth Ave
Spokane, WA 99202
(509) 838-2531

BC/BE PEDIATRICIAN WANTED for semi-rural community 25 miles south of San Francisco to associate with five member Family Practice group. Send inquiry with CV to Lawrence Bruguera, MD, Coastside Medical Clinic, 225 S. Cabrillo Hwy, Ste 100-A, Half Moon Bay, CA 94019.

OPPORTUNITY for full- and part-time Emergency Physicians. Excellent fee-per-patient load ratio. Malpractice paid. Also, Emergency Department/Family Practice positions for urgent care/industrial center. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

POSITION FOR FULL-TIME PHYSICIAN in Family/Occupational Center. Practice setting in El Toro, California. Competitive compensation. Immediate opening. Call Bea Hetrick at (714) 581-3011.

RESEARCH ASSOCIATE. Study molecular aspects of herpes simplex virus latency and pathogenesis in eye; study transactivation of HSV-LAT gene by early gene products; characterize HSV-1 mutants/recombinants in their capacity to produce latency and reactivate; analyze results and prepare papers for publication. Requirements: PhD in Virology and specialized knowledge in pathogenesis of viral infections affecting eye; recombinant DNA including viral mutants; characterization of viral RNA/DNA; Protein Chemistry; ELISA, RIPA, and Western Blotting methods; designing and executing experiments independently. Salary: $26,850 per annum. Job and interview site in Los Angeles, California. Send ad and résumé to Job #DB22037, PO Box 9560, Sacramento, CA 95823-0560, no later than March 31, 1991.

SOUTHERN CALIFORNIA—CLINICAL ALLERGISTS/IMMUNOLOGISTS AND PEDIATRIC PULMONOLOGIST

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for staff positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

WARM AND SUNNY ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 145 plus physicians in 14 clinic locations throughout Arizona has positions available in Family Practice, Internal Medicine, Pediatrics, and Orthopedics. Exceptional fringe benefits, profit sharing, and retirement program. Guarantee for first two years, plus incentive. Early shareholder. Fee-for-service, as well as physician owned HMO. Must be BC/BE. Call or write Bill De Long at Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; 1 (800) 658-9166.

BC/BE NORTHWESTERN CALIFORNIA. OB/GYN needed to join the oldest office in the Redwood area on the north coast. An excellent opportunity for a male or female American trained physician. Excellent compensation and incentive program leading to corporate membership in one year. Three physicians in office but only two doing obstetrics. Send CV and references to T. W. Loring, MD, 2607 Harris St, Ste E, Eureka, CA 95501; (707) 442-4593.

BC/BE RADIOLOGIST. Exceptional northern California location. Diagnostic and interventional fee-for-service practice. All imaging modalities represented. Academic appointment available. Comfortable workload; excellent quality of life. Contact Carol Westfall, Cejka & Company, 222 S. Central Ave, Ste 700, St. Louis, MO 63105; phone 1 (800) 765-3055.

DENVER. There are two young, busy, two-person groups in this high growth suburb of Aurora seeking third members. Also, opportunity to associate with busy, 45 year old Internist next to our 200-bed hospital, or establish practice in fast growing Parker (15 miles south) with financial assistance. Send CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept HH-3, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

OREGON. General Internal Medicine and Family Practice, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

(Continued on Page 360)

(Continued from Page 359)

PHYSICIANS WANTED

COLORADO OR UTAH

Attractive private practice opportunities now exist in both the Denver and Salt Lake City areas:

DENVER, COLORADO – A young, boarded Pediatrician practicing near our 200-bed hospital in the Denver suburbs for the past two years is now seeking an associate.

LAYTON, UTAH – A multi-speciality group here is seeking to add their third Pediatrician. Also, a three-physician group, with two offices, is in need of another member. Layton is 20 miles north of Salt Lake City and 15 miles south of Ogden.

For more information send CV to: Gordon Crawford, Manager, Professional Relations, Humana Inc., Dept. HH-3B, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

PRACTICE OPPORTUNITIES. Family Practice, Internal Medicine, and Obstetrics and Gynecology positions available in San Diego, California, Phoenix, Arizona, Seattle, Washington, and Salt Lake City, Utah. Contact Eric Bennett, PO Box 5316, Scottsdale, AZ 85261; (602) 998-4540.

NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through 1993. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD. EOE/M/F/V/H.

FEMALE PHYSICIAN seeks partner in thriving practice of Primary Care Medicine and office Gynecology. Specializing in personalized health care for women. Located in a delightful, growing community 35 miles from San Francisco. Flexible hours. Contact Bonnie Rathjen, MD, 4102 Moller Dr, Pleasanton, CA 94566; (415) 462-6360 evenings.

PEDIATRICIAN BC/BE. Join established two Pediatrician practice. Monterey bay area of north central California. Salaried position with partnership opportunity. Excellent fringe benefits. Office located adjacent to modern 250-bed hospital. Community of 100,000 plus population. Call rotation divided among five physicians. Send CV to Number 235, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

DENVER. Group and associate solo opportunities exist with busy Family Physicians in the Denver suburbs of Aurora and Thornton. Send CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept HH-3C, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

GREAT OPPORTUNITIES IN NORTHERN CALIFORNIA. We are San Jose's leading multispecialty private group practice, and want a BC/BE physician with broadly based high level training to join our Department of Urgent Care and General Medicine. The position offers competitive salary plus incentive bonus, a comprehensive benefits package including retirement and 401K plan contributions, and early access to partnership and stockholder status. The south bay area provides a wide range of cultural and recreational activities, good schools, fine dining, and a congenial climate. We're growing, and we'd like to hear from you. Send your CV to Maureen Forrester, San Jose Medical Group, 45 S. 17th St, San Jose, CA 95112; or call us at (408) 282-7833.

FAMILY PRACTITIONER. Seattle, Washington suburb. Private practice available with three BC Family Practitioners. Very busy practice. Young physicians. For details, call Eloise Gusman; 1 (800) 535-7698, or send CV to PO Box 1685, Covington, LA 70434-1685.

INTERNAL MEDICINE. Sparks/Reno, Nevada. Opportunity available with established BC Internist. For details, call Eloise Gusman; 1 (800) 535-7698, or send CV to PO Box 1685, Covington, LA 70434-1685.

CALIFORNIA, SOUTHERN—INLAND EMPIRE. Excellent full-time opportunity for BC/BE Emergency Medicine Physician in a high volume (45,000 EM visits per year) medical center. Stable contract, hourly of $100 plus, profit-sharing, highly competitive group supported malpractice coverage and excellent benefits. Opportunity for growth and leadership. Join our partnership of established Ambulatory Care and Emergency Medicine Physicians. Contact John Gravette, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612-3027; (415) 835-7431 or, outside of California (800) 842-2619.

CARDIOLOGY. Invasive Cardiologist join noninvasive; new Cath lab; north bay area. Huge opportunity. Electrophysiologist even better. Résumé to Number 234, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602. ASAP.

PHYSICIANS WANTED

PHYSICIANS RHEUMATOLOGIST

Seeking BC/BE Rheumatologist to staff our busy outpatient clinic. Part-time, flexible hours. This challenging position allows for contact with patients with diversified diagnoses.

For further information, contact:

Brad Maggy at (415) 573-2400

or send your résumé to:

San Mateo County General Hospital
222 W. 39th Ave
San Mateo, CA 94403

AAE/EOE

SAN MATEO COUNTY GENERAL HOSPITAL

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

OREGON. Family Practice opportunity in group practice in scenic area in Oregon's coast range. Within one hour of the ocean, this location offers excellent steelhead fishing, hunting, ranching, etc. Hospital provides complete relocation assistance. Oregon provides tax incentives to physicians in rural practice. Contact Jean Erickson, 305 NE 102nd Ave, Portland, OR 97220; (800) 622-3377.

NEWPORT BEACH. Start up opportunity to Associate with a busy General Internist. Flexible terms. Please send CV to John Homan, MD, 351 Hospital Rd, #411, Newport Beach, CA 92663; (714) 548-1278.

FACULTY POSITIONS. Well established, fully accredited, 18 resident program seeking full-time faculty. Program is affiliated with UC Davis and located in Stockton, California. Candidate must be BC/BE. Teaching and OB experience preferred, but not required. Responsibilities include resident teaching, patient care, administration, and research development. Send CV to Bruce S. Nickols, MD, Family Practice Department, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6834. AA/EOE.

DON'T FORGET!

The deadline for submitting classifieds for the May issue of WJM is March 25. Send your advertisement to:

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San Francisco, CA 94120-7602
(415) 882-3376

(Continued on Page 361)

THE PERMANENTE MEDICAL GROUP NORTHERN CALIFORNIA

QUALITY

STABILITY

LEADERSHIP

GROWTH

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REWARDS

The Permanente Medical Group, the largest multispecialty group practice in the U.S., is undergoing explosive growth in its Northern California region: the San Francisco Bay Area, Sacramento and the Central Valley. Our rapid increase in membership has created practice opportunities throughout the region.

Our physician-managed group is part of the comprehensive Kaiser Permanente Medical Care Program. As a TPMG physician, you have access to the latest medical technology and resources, the support of colleagues in all subspecialties — and the opportunity to provide excellent health care without the burdens of managing a practice.

TPMG offers many benefits: scheduled time off with cross-coverage provided by your colleagues, continuing education, malpractice insurance, a substantial retirement program and special arrangements for physicians transferring from established practice. For complete information, call or send CV to: The Permanente Medical Group, Inc., Richmond Prescott, M.D., Physician Recruitment Services, Dept. WJM-7153, 1814 Franklin, 4th Floor, Oakland, CA 94612. (800) 777-4912. EOE

KAISER PERMANENTE
Good People. Good Medicine.

(Continued from Page 360)

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (415) 601-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

WASHINGTON, PUGET SOUND. Full- or part-time position with expanding physician owned group. Well established, practicing adult Emergency Medicine. High level of Critical Care with excellent medical staff. Great flexibility in scheduling to enjoy the northwest. Partnership potential. Malpractice paid. ABEM certification or preparation required. Send CV to TECP, 955 Tacoma Ave S., Ste 210, Tacoma, WA 98402; (206) 627-2303.

CALIFORNIA, BERKELEY. Experienced Emergency Room, Family Practice, Internal Medicine, and Urgent Care Physicians sought to staff an inpatient service at a large community hospital. Excellent hours (no nights) and compensation. Applicants must be BC/BE in either Emergency Medicine, Family Practice, or Internal Medicine. Job parameters may be configured to accommodate full- or half-time commitments. Please send CV to Joan Wendell, Office Manager, PO Box 5138, Berkeley, CA 94705.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

PHYSICIANS WANTED

SOUTHERN CALIFORNIA NEUROSURGEONS

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for staff positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

ESTHETIC SURGERY—SOUTHERN CALIFORNIA. BC general Plastic Surgeon to associate with ENT. Practice 99% cosmetic. Desire emphasis in breast/body contouring to complement current practice. Send CV to PO Box 3421, Santa Barbara, CA 93120.

BC/BE PULMONARY/CRITICAL CARE—SAN FRANCISCO BAY AREA. Physician sought to join two busy Pulmonologists in Marin county, 10 miles north of San Francisco. Excellent opportunity to be part of a well established practice, which would include inpatient and outpatient consultation and active involvement in the Intensive and Coronary Units at a superb community hospital. Guaranteed salary and benefits are available now but we will be willing to wait for completion of training in 1991. Send CV to Alan Margolin, MD, 900 S. Eliseo Dr, Greenbrae, CA 94904.

FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

PHYSICIANS WANTED

OTOLARYNGOLOGIST WANTED

Two doctor ENT office. Senior member retiring in July of 1991. BC/BE.

Needed in growth area of beautiful northern California.

Allergy and head and neck surgery also provided, as well as Audiology services in office.

Please send your CV with references to:

David L. Williams, MD
3330 Churn Creek Rd, D5
Redding, CA 96002.

Area brochure available upon request.

OB/GYN—Salt Lake City area. Progressive community, excellent cultural and recreational activities. Thriving independent practice in multispecialty group location with excellent coverage. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

COASTAL SOUTHERN CALIFORNIA. Seeking BC/BE Internist with subspecialty in Oncology to join a fast growing multispecialty group practice in north San Diego county. Generous compensation package; competitive salary, malpractice, medical/dental/life/AD&D/disability; wonderful living environment. Please send CV to Physician Recruitment, The Mission Park Medical Clinic, 2201 Mission Ave, Oceanside, CA 92054; or call (619) 967-4892.

(Continued on Page 362)

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PHYSICIANS WANTED

SAN FRANCISCO BAY AREA BC/BE INTERNISTS

We are currently seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 pre-paid health plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city, and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to:

Winslow Wong, MD
Attn: Administration
Kaiser Permanente Medical Center
27400 Hesperian Blvd
Hayward, CA 94545

EOE

ORTHOPEDIC SURGEON. University of California, San Francisco seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position at the Valley Medical Center, Fresno. The Orthopedic Department at VMC supports a busy Trauma Service and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. This position also offers private practice opportunities in a setting within the faculty group. Competitive salary and benefits. The central California location offers affordable and enjoyable year-round recreational living. Address inquiries and CVs to H. B. Morgan, Jr, MD, Chief of Orthopedics, 2212 N. Winery, #130, Fresno, CA 93703. EO/AA employer, women and minorities are encouraged to apply.

FAMILY PRACTICE RESIDENCY FACULTY POSITION—CASPER, WYOMING. University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, BC Pediatrician to be the Pediatric Coordinator of an 8-8-8 Family Practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming. The University of Wyoming is an affirmative action/EOE. Contact Dr David Driggers, Director, University of Wyoming Family Practice Residency, 1522 E. "A" St, Casper, WY 82601; (307) 266-3076.

REDWOOD COAST. Primary Physician for community health center providing quality care to low income population. Excellent hospitals, support services. Supervise midlevels. Unequaled life-style combines spectacular beaches and redwoods with amenities of university town. Contact M. Sterling, HODC, 770 10th, Arcata, CA 95521; (707) 822-2957.

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— FRINGE BENEFITS —

PHYSICIANS WANTED

OCCUPATIONAL MEDICINE PHYSICIAN. Modesto Occupational Medical Clinic is looking for a full-time physician. We are a young, thriving high-volume practice in need of an additional physician who is BC/BE or with experience in Occupational Medicine. We are a full service clinic with x-ray, Physical Therapy, and all equipment for Occupational Monitoring. We have a large client company base with several years of experience. This person must have good clinical skills, be highly motivated, be energetic, and looking for a challenging career. Position may include administrative and clinic responsibilities with opportunity for partnership. We are located in the central valley two hours from both San Francisco and several excellent ski resorts in the Sierra Nevada. Please contact Susan Hooper, 1600 Sunrise, Ste 16, Modesto, CA 95350; (209) 529-6234.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

INTERNIST—Salt Lake City area. Progressive community, excellent skiing, hiking, as well as close proximity to major city. Independent or multispecialty group locations. Outstanding remuneration package. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

FAMILY PHYSICIAN—Salt Lake City area. Progressive community, outstanding recreational and cultural activities, diverse physician backgrounds, thriving practice. Independent or multispecialty group locations. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

DENVER. Extremely busy, five physician group with three Denver area offices are now seeking their fourth Neurologist. Two members are Neurosurgeons. Send CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept HH-3A, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

PEDIATRICIAN, BC/BE to join group Family Practice/Pediatrics. Growing community with growing pediatric population. Active Nursery Level II hospital and nursery with NNP coverage. Offering competitive salary, equal call schedules, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

MEMORIAL CLINIC offers excellent opportunity for BC/BE Family Practitioner to establish a second Family Practice neighborhood clinic. OB optional. Competitive salary and excellent benefits. Send CV to Memorial Clinic, Attention Inge Hart, 500 Lilly Rd, N.E., Olympia, WA 98506; (206) 456-1122, ext 249.

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PHYSICIANS WANTED

IMMEDIATE OPENING. BC, recently eligible, Internal Medicine. Assume substantial practice in three person group adjacent to Tri-City Hospital, Oceanside, California. Call (619) 724-8683.

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and has an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is a Paramedic Base Station and Training Center, and in addition, has an active Helicopter Service and Regional Poison Center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after April 30, 1991. The University of California is an Affirmative Action/Equal Opportunity Employer.

DENVER. Primary Care Physician for geriatric adults and one BC/BE Internist. $74,294 plus benefits, faculty appointment. Contact: R. J. Brooks, MD, Assoc Director, FLMHC, 3520 W. Oxford Ave, Denver, CO 80236; (303) 762-4117. AA/EOE.

CALIFORNIA. Excellent Ambulatory Care and Emergency Medicine positions for BC/BE physicians. Northern, southern, and central locations. Stable contracts, high hourlies, attractive facilities, profit-sharing, paid malpractice, excellent benefits. Opportunity for growth and leadership. Join our partnership of established Ambulatory Care and Emergency Medicine Physicians. Contact John Gravette, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612-3027; (415) 835-7431 or, outside of California (800) 842-2619.

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Southwest Medical Associates is a large, rapidly growing multi-specialty group in Las Vegas, Nevada, and we are seeking a second Oncologist BC/BE. We offer an HMO and FFS patient mix and C-COP (NSA BP, CALGB, RTOG) and university teaching hospital affiliation is available. In addition, we have excellent starting salaries and a generous comprehensive benefits package.

If you are interested in this exceptional opportunity, **please contact Jerry Reeves, M.D., President, Southwest Medical Associates, P.O. Box 15645, Las Vegas, NV 89114.** Equal Opportunity Employer.

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(Continued on Page 363)

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Los Angeles County

There are now several, attractive private practice opportunities for an OB/GYN to join established, growing practices in the western San Fernando Valley.

An aggressive two-physician group practicing here for eight years is now seeking another member, and a respected solo OB/GYN is also in need of an associate.

These physicians are board-certified and have their offices adjacent to our 236-bed hospital.

If you would like to investigate these opportunities, send your curriculum vitae to: Gordon Crawford, Manager, Professional Relations, Humana Inc., Dept. HH-3, 500 West Main Street, Louisville, KY 40201-1438.

Humana®

(Continued from Page 362)

PHYSICIANS WANTED

EMERGENCY PHYSICIAN. Immediate opening; competitive salary, occurrence insurance. New facility, low volume Emergency Department. Rural location, excellent outdoor recreation; hunting, fishing, hiking, skiing. ACLS/ATLS required. Send CV to Steven P. French, MD, 190 Arrowhead, Evanston, WY; or call (307) 789-3636.

MEDICAL DIRECTOR. Family Practice Physician (BC/BE) for community based clinic. Emphasis Family Planning, Primary Care, Pediatrics, STD and health education. Responsibile for medical policy, QA, and supervision of clinical staff. Bilingual/cultural Hispanic preferred. Inquiries to EVCC, 2470 Alvin Ave, #3, San Jose, CA 95121. EOE.

SEATTLE, Washington suburban 26 physician primary care group has immediate need for Family Physicians and Internists. Area growth has created the need for a team physician who enjoys work as well as play in the beautiful (and affordable) Pacific northwest. Remuneration includes salary, bonus, and fringe benefit package. For more information, please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

ALASKA. The only Vitro-Retinal specialist in Anchorage is now seeking an associate with similar skills. For more information send CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept HH-3, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

SOUTHERN CALIFORNIA EMERGENCY PHYSICIANS

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for staff positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

INTERNIST BC/BE. Current associate leaving for academic position. Busy Internal Medicine practice available July 1991. Currently netting $155K, on call every seventh weekend. If you desire to enjoy life while maintaining a fully established and challenging practice send CV to Cecil Bullard, MD, 5339 N. Fresno, #107D, Fresno, CA 93710.

EMERGENCY MEDICINE. Emergency Medicine group seeking career oriented ACLS, ATLS certified physician for an immediate opening. Moderate volume; income $140,000 plus. Great outdoor activities including hunting, fishing, boating, skiing, sailing, camping, and hiking in south central Washington on the Columbia River. Send CV to Kennewick Emergency Physicians, PS, PO Box 6192, Kennewick, WA 99336-6192; or call (509) 627-1798.

COLORADO. BC/BE INTERNIST to join three Internists in multispecialty group. Excellent opportunity for person interested in rural living, mountain recreation, and health care for medically underserved population. Send CV to Marguerite Salazar, 204 Carson Ave, Alamosa, CO 81101; (719) 589-5161.

SAN JOAQUIN VALLEY. Excellent opportunity for Family Practitioner to serve the underserved. No night call or weekends. Competitive salary plus benefits, paid malpractice. Agricultural community, one hour from the mountains, two hours from the coast. Bilingual English-Spanish helpful. Send CV to Hugh F. Stallworth, MD, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

WASHINGTON, PUGET SOUND. Part- or full-time Emergency Department practice with low volume, excellent medical staff, and great freedom of scheduling. Malpractice paid. Independent contractor. Send CV to TECP, 955 Tacoma Ave S., Ste 210, Tacoma, WA 98402.

GENERAL INTERNIST IN THE PACIFIC NORTHWEST. Busy 30 doctor multispecialty group practice looking for General Internist with ICU skills and interests to join an existing Internal Medicine department. Competitive salary and benefits; ownership status available after 18 months of employment. Send CV to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

23 PHYSICIAN GROUP PRACTICE. Recent population growth and demand have created the need for several specialists including OB/GYN, Family Practice, Internal Medicine, Cardiology, and Pediatrics in this 23 physician group practice. Situated 60 miles east of San Francisco, the group serves a local population of 35,000. Nearby skiing and boating, reasonable housing, and an excellent school system. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

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PHYSICIANS WANTED

CALIFORNIA
FAMILY PRACTICE
INTERNAL MEDICINE
SURGEON and PEDIATRIC

physicians to join Family Walk-In Medical Centers staff, a growing health care provider with five medical centers in Fresno, California, which is located in the Central San Joaquin Valley. Fresno metropolitan area has a population of over 400,000. Easy access to major metropolitan areas, Pacific coast and the Sierras. Salary guarantee of $100K to $120K for Family Practice, Internal Medicine, and Pediatric physicians; $150K for Surgeons, or equal to an average of the last two years' earnings, whichever is greater. Malpractice paid. Excellent working conditions. Contact:

D. Duane Oswald
Family Walk-In Medical Centers
PO Box 27680
Fresno, CA 93729-7680

BC/BE FAMILY PRACTITIONER. OB-competent, for nonprofit community clinic in California redwood country. Rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

JUNIOR FACULTY INTERNIST. University of California, San Francisco, Valley Medical Center, Fresno Medical Education Program, Department of Family Practice seeks recent BE Internal Medicine graduate to attend on a general Internal Medicine ward, teach in the ambulatory setting and contribute to the intellectual life of the Department. Our full-time experienced Senior Internist will provide faculty development, consultation, and backup. VMC is a major affiliate of UCSF School of Medicine sponsoring several well regarded programs, including Internal Medicine. Delightful and affordable central California location. Salary guarantee and faculty practice plan incentive. Available July 1, 1991. Send CV to Robert Heiligman, MD, Assistant Chief of Family Practice, 2212 N. Winery, #130, Fresno, CA 93703. EOE, women and minorities are encouraged to apply.

MEDICAL DIRECTOR TRAUMA SERVICES. Eden Hospital. Level II Regional Trauma Center, Alameda county. Available December 1, 1990. Submit CV to Trauma Services, Eden Hospital, 20103 Lake Chabot Rd, Castro Valley, CA 94546; or call Dr Peter Wong, (415) 886-0535 or Dr Brian Walker, (415) 881-8445.

FAMILY/GENERAL PRACTICE POSITION. We are looking for a Family/General Practitioner to join a progressive small group practice in Berkeley, California, serving a very diverse patient population. We practice a wide range of adult medicine, general hospital medicine, office Pediatrics and Gynecology. There is no Obstetrics. Work hours are flexible and range from half- to full-time. The starting date and salary are negotiable. Minorities and women encouraged. Contact Linda Spangler, MD, Alcatraz Ave Medical Group, 1650 Alcatraz Ave, Berkeley, CA 94703; (415) 652-8680.

SOUTHERN CALIFORNIA
HEAD AND NECK SURGEONS

Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for both staff and chief positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, 393 E. Walnut, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

PHYSICIANS WANTED

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ALASKA. A 10 physician multispecialty group in Anchorage is now seeking to add their second Neurologist. For more information send CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept HH-3A, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

CENTRAL CALIFORNIA. Hospital based teaching opportunity for OB/GYN in a new residency program at the KMC. Ideal candidate is a team player with a strong desire to teach residents. This UCLA affiliate has a busy OB department with 5,000 deliveries per year. Please contact Mary Letterii, Vice President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

INTERNIST. Immediate opening. Large, established, rapidly growing Los Angeles medical facility. High salary. Full benefits. Malpractice insurance paid. Contact Mr Miller; (213) 384-2504.

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Elaine Nelson (209) 255-0854

PEDIATRICIAN—Salt Lake City area. Progressive community, excellent cultural and recreational opportunities. Thriving multispecialty practice or solo practice location. Top remuneration. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

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Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

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PHYSICIANS WANTED

HEMATOLOGIST
ONCOLOGIST
ENDOCRINOLOGIST
NEUROLOGIST

Multispecialty group practice located in the Puget Sound area. Please send CV with reply to:

Number 212
Western Journal of Medicine
PO Box 7602
San Francisco, CA 94120-7602

SAN FRANCISCO BAY AREA. An Internist practicing in an east bay community of 75,000 is seeking an Internist to take over his 35-year-old practice which numbers 400-500 patients. Send your CV to Gordon Crawford, Manager, Professional Relations, Humana Inc, Dept HH-3B, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

FULL TIME MD POSITION AT THE LEVEL OF ASSISTANT/ASSOCIATE PROFESSOR OF CLINICAL FAMILY PRACTICE available in the Department of Family Practice, University of California, Davis. Must be BC by the American Board of Family Practice with interest, training, and/or experience in administration, teaching, research, academic publication, and Obstetric activities. The position will remain open until May 31, 1991. Send CV with list of three to five references to Robert C. Davidson, MD, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd, Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer.

OB/GYN—SOUTHERN CALIFORNIA. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

PEDIATRICIANS—SOUTHERN CALIFORNIA. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

RADIOLOGIST needed to perform state-of-the-art Diagnostic Radiology. Salary $100,000 per year. Minimum requirements are an MD degree, Radiology Board Certification, Utah Physician Surgeon License, and ability to perform MRI, Cardiac Ultrasound, selective Angiography, and invasive procedures requiring Angiography. Job located in Tooele County and Salt Lake County, Utah. Contact D. Michael Edson, MD, President, Consultant Radiologists, 3460 S. Pioneer Parkway, West Valley City, UT 84120.

FAMILY PRACTICE-HOSPITAL SPONSORED CLINIC OPPORTUNITY. Dynamic, growth oriented hospital in beautiful north central Wisconsin is seeking Family Physicians to join a growing practice in a new facility. The administrative burdens of medical practice will be minimized in this hospital managed clinic. The hospital has committed to an income and benefit package which is significantly higher than similar opportunities. Package includes base income, incentive bonus, malpractice, disability, signing bonus and student loan reduction/forgiveness program. All relocation costs will be borne by the hospital. Please contact Kari Wangsness, Associate, The Chancellor Group, Inc, France Place, Ste 920, 3601 Minnesota Dr, Bloomington, MN 55435; (612) 835-5123.

SOUTHERN CALIFORNIA. 300-bed hospital in growth community at foothills of Mt Baldy. Opportunity for OB/GYN, Family Practice, and Rheumatologist to associate with successful practitioners. Hospital will provide generous guarantee, moving expenses, and practice management assistance. Please contact Ken Baker, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

OBSTETRICS/PEDIATRICS. Small multispecialty group seeks second Pediatrician and OB/GYN to work with present physicians. Excellent compensation and benefits. Looking for long-term partnership. Call or send CV to Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

INTERNAL MEDICINE. Full-time BC/BE Internist for multispecialty group in southeast Los Angeles. Office/hospital and consulting practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for partnership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

FAMILY PRACTITIONER. Full-time, BC/BE for growing multispecialty medical group in southeast Los Angeles. Some Spanish helpful. Top salary, benefits, and malpractice. Partnership potential second year. Send CV or call Craig Kaner, Administrator, All Care Medical Group, 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

INTERNIST WANTED. Internal Medicine physician wanted to join an Internal Medicine group in San Diego, California. Guarantee plus commission, opportunity to join full partnership in two years. Reply to Number 231, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

THE DIVISION OF FAMILY MEDICINE at the UCSD School of Medicine is recruiting physicians to staff clinical practices and to provide clinical supervision to residents and medical students at a variety of locations in San Diego county. Candidates should be BC in Family Medicine and licensed or eligible for licensure in the state of California. Responsibilities will include direct patient care. Salaries are competitive and commensurate with experience and qualifications. Candidates should send a CV and names of three references to David M. Baughan, MD, Director of Clinical Services, Division of Family Medicine (0807) UCSD, 9500 Gilman Dr, La Jolla, CA 92093-0807. The University of California, San Diego is an Equal Opportunity/Affirmative Action Employer.

FAMILY PRACTICE—FRESNO. Family Practice, Emergency Room, Occupational Medicine Physician BC/BE to join expanding group to provide Family Medicine, Occupational Medicine, and Urgent Care Medicine in a well equipped clinic setting. Competitive salary with incentive plan, paid malpractice. Send CV to Medical Director, 3636 N. First St, Ste 162, Fresno, CA 93726; (209) 221-2022.

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DENVER—INTERNIST. A busy two physician group, established in high-growth suburb since 1976, is now seeking a third member. For more information, send CV to Gordon Crawford, Professional Relations, Humana Inc, Dept HH-3B, 500 W. Main St, Louisville, KY 40201-1438; or call toll-free 1 (800) 626-1590.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 6-8, 1991, Loews Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 8-13, 1991, Bally's Grand Hotel, Reno.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 20-22, 1991, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-13, 1991, Westin Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-27, 1991, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-4, 1991, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1991, Quail Lodge, Carmel, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-10, 1991, The Marshall Building, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): April 26-28, 1991, Salisham.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 11-13, 1991, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, 1991, Red Lion, Bellevue.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 13-15, 1991, Jackson Lake Lodge, Moran.

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ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
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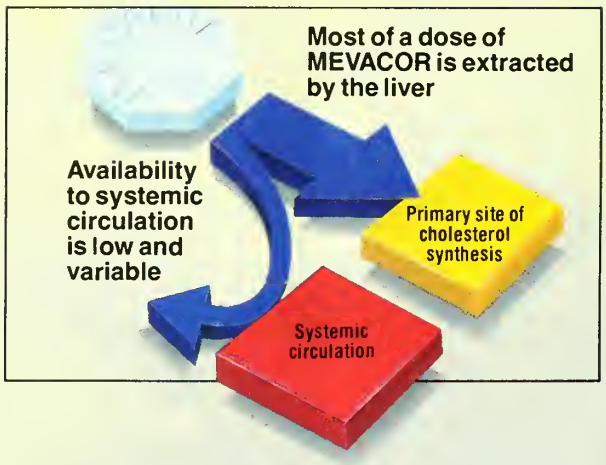

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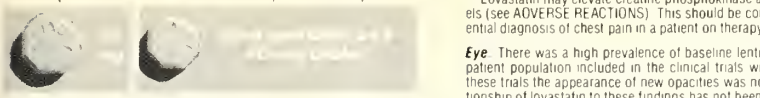
(LOVASTATIN | MSD)



CONTRAINDICATIONS: Hypersensitivity to any component of this medication

Active liver disease or unexplained persistent elevations of serum transaminases

Pregnancy and lactation

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction*. **Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS).** When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle. **Several cases of rhabdomyolysis have been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥ 1 g/day) of nicotinic acid. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness, or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General*: Before instituting therapy with MEVACOR® (Lovastatin, MSD), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Eye: There was a high prevalence of baseline lenticular opacities in the patient population included in the clinical trials with lovastatin. During these trials the appearance of new opacities was noted. The causal relationship of lovastatin to these findings has not been established.

Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase. There was no clinically significant change in visual acuity in the patients who had new opacities reported, nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity. Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastatin therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin*: See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg/b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (1.2 5 and 6.2 5 times the maximum recommended human dose).

A statistically significant increase ($p \leq 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose), no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (1.2 5 or 6.2 5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (6.2 5 and 312 times the maximum recommended human dose), no increase was seen at a dosage of 20 mg/kg/day (1.2 5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region. Acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat, however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadjusted $p = 0.025$). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose – about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers: Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin, MSD) is generally well tolerated. Adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR, about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences: Adverse experiences reported in patients treated with MEVACOR in controlled clinical studies are shown in the table below:

	MEVACOR (N = 613) %	Placebo (N = 82) %	Cholestyramine (N = 88) %	Probucol (N = 97) %
Gastrointestinal				
Constipation	4.9	—	34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9	—	13.6	3.1
Flatus	6.4	2.4	21.6	2.1
Abdominal pain/cramps	5.7	2.4	5.7	5.2
Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1.0
Headache	9.3	4.9	4.5	8.2
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	3.1
Dysgeusia	0.8	—	1.1	—

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine 9% and probucol 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

Uncontrolled Clinical Studies: The adverse experiences observed in uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function tests were observed at a higher incidence than in the controlled studies (see WARNINGS, *Liver Dysfunction*). Myopathy (myalgia with marked CPK elevations) was reported in approximately 0.5% of patients (see WARNINGS, *Skeletal Muscle*).

Causal Relationship Unclear: *Nervous System*: Peripheral neuropathy has been reported; the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

Special Senses: Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase (see PRECAUTIONS).

Post-marketing Experience: Additional adverse experiences occurring since the drug was marketed are listed below:

Clinical Adverse Experiences

Gastrointestinal: Hepatitis, cholestatic jaundice, anorexia, vomiting.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, flushing, malaise, and dyspnea.

Nervous System/Psychiatric: Psychic disturbances, including anxiety, paresthesia.

Skin: Erythema multiforme, including Stevens-Johnson syndrome, toxic epidermal necrolysis.

Causal Relationship Unknown

Gastrointestinal: Pancreatitis, stomatitis.

Skin: Alopecia.

Nervous System/Psychiatric: Depression, insomnia.

Metabolic: Edema.

Clinical Laboratory Test Findings

Liver Function Tests: Liver function test abnormalities, including elevated alkaline phosphatase and bilirubin.

Thyroid Function Tests: Rare reports of thyroid function test abnormalities in patients taking concomitant thyroxine.

OVERDOSAGE: The oral LD_{50} of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* for dose response results).

For those patients with severely elevated serum cholesterol levels (i.e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at 40 mg/day.

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), the maximum recommended dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

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For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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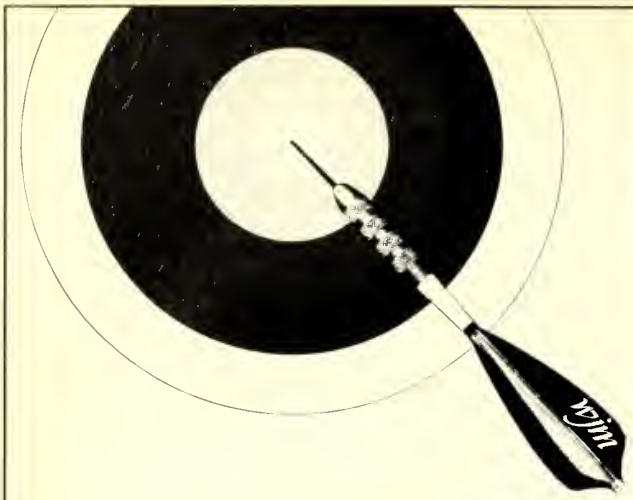

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From the Department of Internal Medicine, Division of Endocrinology, Mayo Clinic, Rochester, Minnesota.

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For Brief Summary, please see following page.

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References: 1. Newton RE, *et al* A review of the side effect profile of buspirone *Am J Med* 1986,80(3B) 17-21 2. Luckhi, *et al* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function *Br J Clin Pharmacol* 1987,23 207-211 3. Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987,82(5A) 20-26

Contraindications: Hypersensitivity to buspirone hydrochloride
Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended BuSpar should not be employed in lieu of appropriate antipsychotic treatment
Precautions: General—*Interference with cognitive and motor performance.* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol
Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.
Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia) Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia)
Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding, and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them
Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**) Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers The clinical significance is not clear Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid
Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice, buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur
Pregnancy: Teratogenic Effects—Pregnancy Category B Should be used during pregnancy only if clearly needed
Nursing Mothers—Administration to nursing women should be avoided if clinically possible
Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age
Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg
Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.
Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement
Associated with Discontinuation of Treatment—The more common events causing discontinuation included central nervous system disturbances (3 4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1 2%), primarily nausea, miscellaneous disturbances (1 1%), primarily headache and fatigue. In addition, 3 4% of patients had multiple complaints, none of which could be characterized as primary
Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials *Cardiovascular* Tachycardia/palpitations 1% *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2% *EENT* Blurred vision 2%. *Gastrointestinal* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal* Musculoskeletal aches/pains 1% *Neurological* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1% *Skin* Skin rash 1% *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%
Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows Frequent are those occurring in at least 1/100 patients, infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients *Cardiovascular*—frequent nonspecific chest pain; infrequent syncope, hypotension, hypertension, rare cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia *Central Nervous System*—frequent dream disturbances, infrequent depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis *EENT*—frequent tinnitus, sore throat, nasal congestion, infrequent redness and itching of the eyes, altered taste, altered smell, conjunctivitis, rare inner ear abnormality, eye pain, photophobia, pressure on eyes *Endocrine*—rare galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding, rare burning of the tongue *Genitourinary*—infrequent urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare amenorrhea, pelvic inflammatory disease, enuresis, nocturia *Musculoskeletal*—infrequent muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias *Neurological*—infrequent involuntary movements, slowed reaction time, rare muscle weakness *Respiratory*—infrequent hyperventilation, shortness of breath, chest congestion, rare epistaxis *Sexual Function*—infrequent decreased or increased libido, rare, delayed ejaculation, impotence *Skin*—infrequent edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters, rare acne, thinning of nails *Clinical Laboratory*—infrequent increases in hepatic aminotransferases (SGOT, SGPT), rare eosinophilia, leukopenia, thrombocytopenia *Miscellaneous*—infrequent weight gain, fever, roaring sensation in the head, weight loss, malaise, rare alcohol abuse, bleeding disturbance, loss of voice, hiccoughs
Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.
Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance
Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior)
Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage
Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage No specific antidote is known and dialyzability of buspirone has not been determined
For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative
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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:
1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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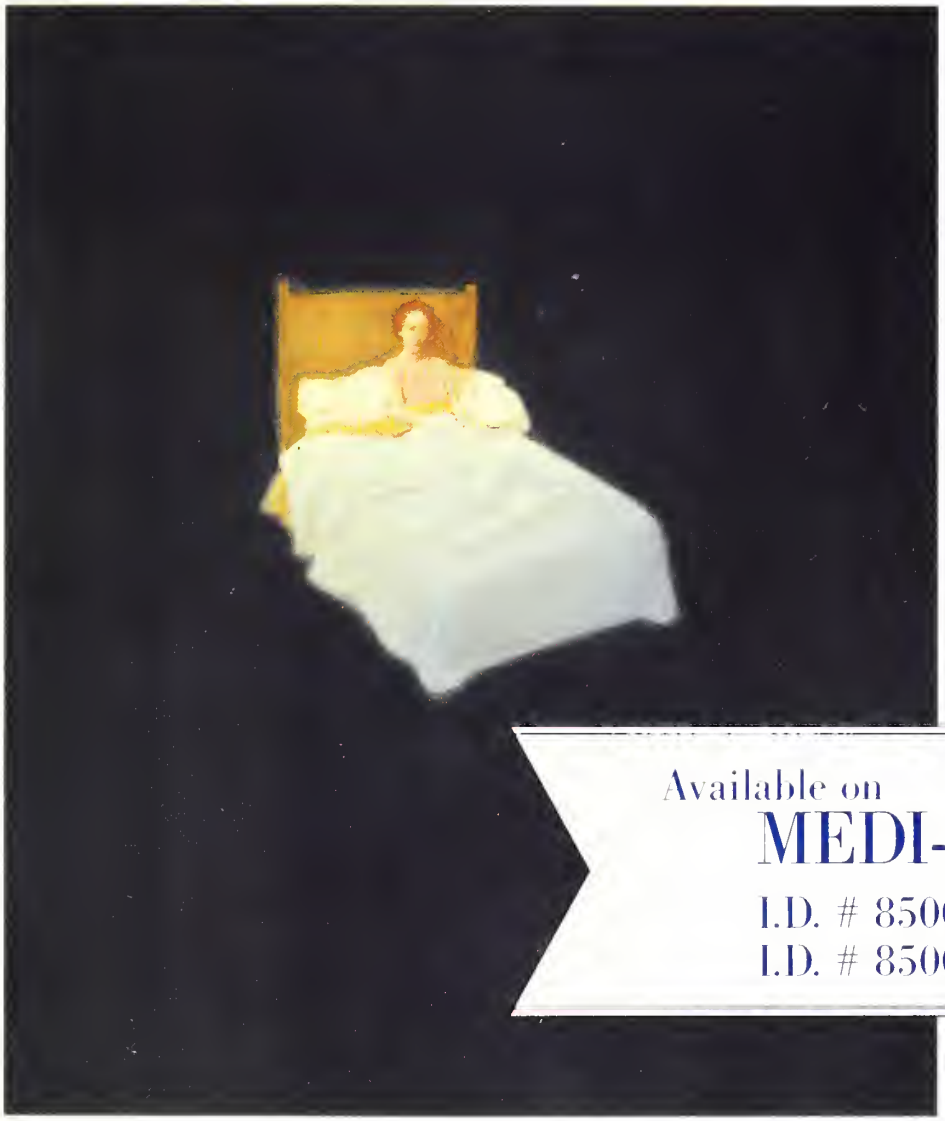

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- A clear return to morning

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References:

1 Lamphere J, Roehrs T, Zorick F, Koshorek G, Roth T Chronic hypnotic efficacy of estazolam *Drugs Exp Clin R* 1986,12(8) 687-691
2 Pierce MW, Shu VS Efficacy of estazolam The United States clinical experience *Am J Med* 1990,88(3A) 6S
3 Walsh JK, Targum SD, Pegram V, et al A multi-center clinical investigation of estazolam short-term efficacy *Curr Ther Res* 1984,36(5) 866-874
4 Dominguez RA, Goldstein BJ, Jacobson AF, Steinbook RM Comparative efficacy of estazolam, flurazepam, a placebo in outpatients with insomnia *J Clin Psychiatry* 1986,47(7) 362-365
5 Roehrs T, Zorick F, Lord N Koshorek GL, Roth T Dose-related effects of estazolam on sleep of patients with insomnia *J Clin Psychopharmacol* 1983,3(3) 152-156
6 Pierce MW, Shu VS, Groves LJ Safety of estazolam The United States clinical experience *Am J Med* 1990,88(3A) 12S-17S
7 Scharf MB, Mayleben OW, Fletcher KA, Shu VS, Pierce MW Effect of single doses of estazolam and triazola memory function in adult insomniacs Submitted for publication

Brief Summary

CLINICAL PHARMACOLOGY:

The range of estimates for the elimination half-life varied from 10 to 24 hours Benzodiazepine clearance is accelerated in smokers compared to nonsmokers, and there is evidence that this occurs with estazolam This decrease in half-life, presumably due to enzyme induction by smoking, is consistent with other drugs with simi hepatic clearance characteristics In all subjects the mean elimination half-life appears to be independent of tl dose

CONTRAINDICATIONS:

Contraindicated in pregnant women due to potential fetal damage Women of childbearing age should be wari the potential risk to the fetus

WARNINGS:

Due to CNS-depressant effects patients should be cautioned against engaging in hazardous occupations requi complete mental alertness and about possible combined effects with alcohol and other CNS-depressant drugs

As with all benzodiazepines, amnesia, paradoxical reactions, and other adverse behavioral effects may occu

There have been reports of withdrawal symptoms of the type associated with CNS depressants following ra decrease or abrupt discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE)

PRECAUTIONS:

General Impaired motor and/or cognitive performance attributable to accumulation of benzodiazepines and ac metabolites is a concern in certain patients (eg, those sensitive to benzodiazepines or those with a reduced ca to metabolize and eliminate them) (see DOSAGE AND ADMINISTRATION) Elderly or debilitated patients and t with impaired renal or hepatic function should be advised to monitor themselves for signs of excessive sedatio impaired conditions

May cause dose-related respiratory depression that is ordinarily not clinically relevant at recommended dos patients with normal respiratory function Monitor patients with compromised respiratory function appropriate

Administered with caution to patients exhibiting symptoms of depression Suicidal tendencies and intention overdosage is more common in such patients

Information for Patients Inform patients about consumption of alcohol and other drugs, possible fetal damage excretion in breast milk, hazards of operating machinery or driving, not increasing dose, and worsening of slee after abrupt discontinuation

Laboratory Tests Not ordinarily required in healthy patients When treatment is protracted, periodic blood cou urinalysis, and blood chemistry analyses are advisable

Drug Interactions Benzodiazepines may be potentiated by anticonvulsants, antihistamines, alcohol, barbiturat monoamine oxidase inhibitors, narcotics, phenothiazines, psychotropic medications, or other drugs that produ CNS depression Smokers have increased clearance of benzodiazepines (see CLINICAL PHARMACOLOGY)

Carcinogenesis, Mutagenesis, Impairment of Fertility Two-year carcinogenicity studies were conducted in mice ar at doses of 0 8, 3, and 10 mg/kg/day and 0 5, 2, and 10 mg/kg/day, respectively Evidence of tumorigenicity was n observed Hyperplastic liver nodules were increased in female mice given mid- and high doses The significance o nodules in mice is not known *In vitro* and *in vivo* mutagenicity tests did not show a mutagenic potential Fertility and female rats was not affected by doses up to 30 times the usual recommended human dose

Pregnancy May cause fetal damage if administered during pregnancy The child born of a mother taking benzodiazepines may be at risk for withdrawal symptoms and neonatal flaccidity during the postnatal period

Labor and Delivery No established use

Nursing Mothers Use in nursing mothers is not recommended

Pediatric Use Safety and effectiveness below the age of 18 not established

Geriatric Use Approximately 18% of patients studied were 60 years or older The adverse event profile did no differ from that observed in younger individuals Exercise care when prescribing to small or debilitated elderly patients (see DOSAGE AND ADMINISTRATION)

ADVERSE REACTIONS:

During clinical trials in which ProSom was administered to 1277 patients, the most commonly observed adve events were somnolence, hypokinesia, dizziness, and abnormal coordination The events listed below were al observed Although these events occurred during treatment with ProSom, they were not necessarily caused b

Body as a Whole abdominal pain, allergic reaction, asthenia, back pain, body pain, chest pain, chills, eder fever, headache, jaw pain, lower extremity pain, malaise, neck pain, swollen breast, upper extremity pain; *Cardiovascular System* arrhythmia, flushing, palpitation, syncope, *Digestive System* constipation, decreased appetite, dry mouth, dyspepsia, enterocolitis, flatulence, gastritis, increased appetite, melena, mouth ulcerati nausea, vomiting, *Endocrine System* thyroid nodule, *Hematologic and Lymphatic System* leukopenia, purpura swollen lymph nodes, *Metabolic/Nutritional Disorders* increased SGOT, thirst, weight gain, weight loss, *Musculoskeletal System* arthralgia, arthritis, muscle spasm, myalgia, stiffness, *Nervous System* agitation, amnesia, anxiety, apathy, ataxia, circumoral paresthesia, confusion, coordination abnormal, decreased libido, decreased reflexes, depression, dizziness, dream abnormal, emotional lability, euphoria, hallucinations, hang- hostility, hypokinesia, nervousness, neuritis, nystagmus, paresthesia, seizure, sleep disorder, somnolence, stu thinking abnormal, tremor, twitch Minor changes in EEG patterns, usually low-voltage fast activity, were obs during therapy or withdrawal and are of no known clinical significance, *Respiratory System* asthma, cold syn cough, dyspnea, epistaxis, hyperventilation, laryngitis, pharyngitis, rhinitis, sinusitis, *Skin and Appendages* a dry skin, pruritis, rash, sweating, urticaria, *Special Senses* abnormal vision, decreased hearing, diplopia, ear eye irritation, eye pain, eye swelling, perverse taste, photophobia, scotomata, tinnitus, *Urogenital System* fr urination, hematuria, menstrual cramps, nocturia, oliguria, penile discharge, urinary hesitancy, urinary incont urinary urgency, vaginal discharge/itching, *Postintroduction Reports* Voluntary reports from non-US postmarke experience have included rare occurrences of photosensitivity and agranulocytosis Due to the uncontrolled natur these reports, a casual relationship has not been determined

DRUG ABUSE AND DEPENDENCE:

Controlled Substance Schedule IV *Abuse and Dependence* Withdrawal symptoms have occurred following discontinuation of benzodiazepines Symptoms range from mild dysphoria and insomnia to abdominal and m cramps, vomiting, sweating, tremors, and convulsions Patients with a history of seizures are at increased ris Withdraw gradually in patients taking benzodiazepines for a prolonged period Monitor addiction-prone patie closely

DOSAGE AND ADMINISTRATION:

Initial dose for adult and healthy elderly patients is 1-2 mg at bedtime Increase dose carefully in the elderly Consider an initial dose of 0 5 mg in small or debilitated older patients

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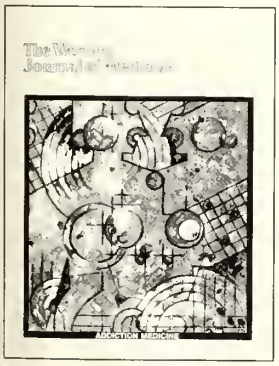

May 1990

A Special Issue of **The Western Journal of Medicine** featuring

- Overview of Addiction Medicine *David Smith, Editor/Founder, Haight-Ashbury Free Clinic*
- Chemical Dependence and Drug Testing in the Workplace *John Osterloh and Charles Becker*
- The New Disease Model of Alcoholism *John Wallace*
- Cognitive Impairment in Abstinent Alcoholics *George Fein, et al*
- Pulmonary Complications of Smoked Substance Abuse *Donald Tashkin*
- Addiction in Adolescents *Martha Morrison*
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From the Cardiology Division and Department of Medicine, Stanford University School of Medicine, Stanford, California. Dr Blake is currently with the New Mexico Heart Clinic, Albuquerque.

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Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

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5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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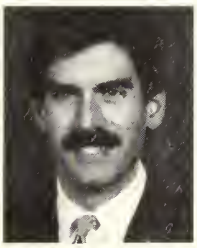
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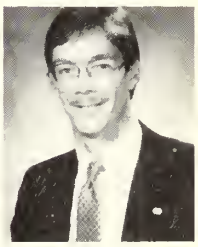
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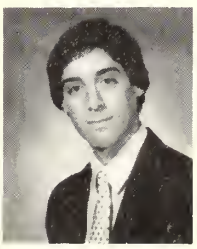
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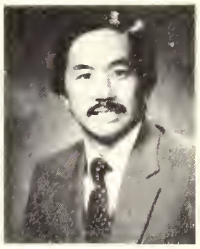
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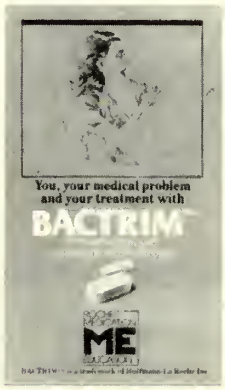

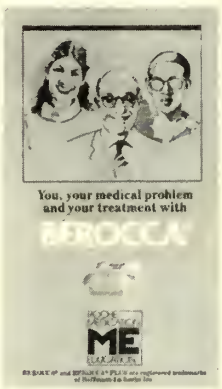

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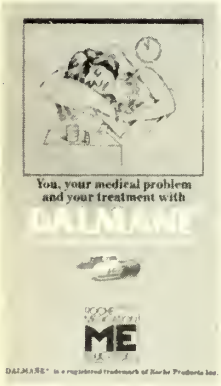

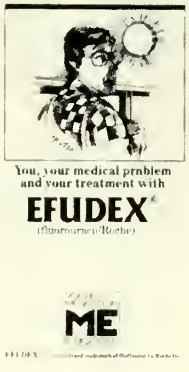

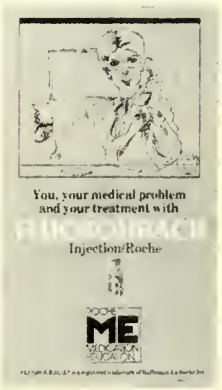

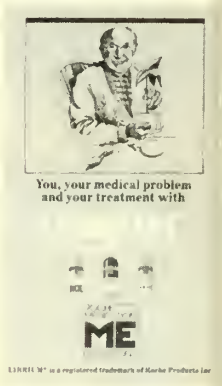

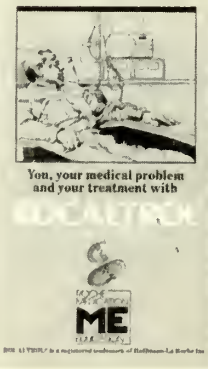

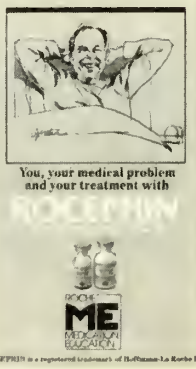

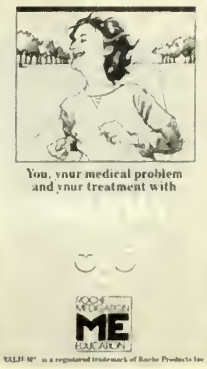

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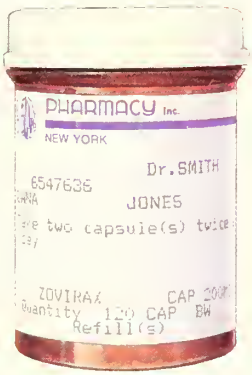

*Alternate maintenance regimens range from 200 mg t.i.d. to 200 mg five times daily.

†In a controlled study of 3 years' duration, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively.[3]

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BRIEF SUMMARY

INDICATIONS AND USAGE: Zovirax Capsules and Suspension are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients

Zovirax Capsules and Suspension are also indicated for the acute treatment of herpes zoster (shingles)

Genital Herpes Infections: The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement These factors should determine patient management, which may include symptomatic support and counseling only or the institution of specific therapy The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs Thus orally administered Zovirax is not appropriate in treating all genital herpes infections The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes)

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing The duration of pain and new lesion formation was decreased in some patient groups The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy Patients with mild disease may derive less benefit than those with more severe episodes In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax

Recurrent Episodes

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered Zovirax given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively Serial analyses of the 3 month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time

The frequency and severity of episodes of untreated genital herpes may change over time After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy Some patients such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year

Chronic suppressive therapy is most appropriate when in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects In general, orally administered Zovirax should not be used for the suppression of recurrent disease in mildly affected patients Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease Thus, this regimen should be considered only for appropriate patients with annual re-evaluation

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions

Herpes Zoster Infections: In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to Zovirax and 94 to placebo), Zovirax (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to Zovirax and 43 to placebo), Zovirax (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia)

CONTRAINDICATIONS: Zovirax Capsules and Suspension are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations

WARNINGS: Zovirax Capsules and Suspension are intended for oral ingestion only

PRECAUTIONS: **General**: Zovirax has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility) The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION)

Exposure of Herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients The relationship between the *in vitro* sensitivity of Herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY Microbiology)

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve Urinary excretion and renal clearance were correspondingly reduced The clinical effects of this combination have not been studied

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes) Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics)

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay

Acyclovir was tested in two *in vitro* cell transformation assays Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice Acyclovir was negative (40 to 80 times human levels) in the other possibly less sensitive, transformation assay

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters, higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels) In addition no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels) In all 4 microbial assays, no evidence of mutagenicity was observed Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in man At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels Results in the other five mammalian cell loci follow at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels, at 2 other loci in mouse lymphoma cells no evidence of mutagenicity was observed at concentrations at least 1500 times human levels

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day p o) or in rats (25 mg/kg/day s c) In the mouse study plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels At a higher dose in the rat (50 mg/kg/day, s c), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size In female rabbits treated subcutaneously with acyclovir subsequent to mating there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels) No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels) In a rat peri- and postnatal study at 50 mg/kg/day s c (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12 5 mg/kg/day and 25 mg/kg/day s c The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured) However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy Plasma levels were not measured in the one month study and were 24 to 48 times human levels in the six month study Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day, some evidence of recovery of sperm production was evident 30 days postdose Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels No testicular abnormalities were seen in dogs given 50 mg/kg/day i v for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels)

Pregnancy: ***Teratogenic Effects***: Pregnancy Category C Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p o), rabbit (50 mg/kg/day, s c and i v) or in standard tests in the rat (50 mg/kg/day s c) These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity In this test rats were given 3 s c doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels There are no adequate and well-controlled studies in pregnant women Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of Zovirax and ranged from 0 6 to 4 1 times corresponding plasma levels These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0 3 mg/kg/day Caution should be exercised when Zovirax is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Herpes Simplex: ***Short-Term Administration***: The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with orally administered Zovirax were nausea and/or vomiting in 8 of 298 patient treatments (2 7%) and headache in 2 of 298 (0 6%) Nausea and/or vomiting occurred in 2 of 287 (0 7%) patients who received placebo

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with orally administered Zovirax (0 3%), included diarrhea, dizziness, anorexia, fatigue, edema skin rash, leg pain, inguinal adenopathy, medication taste and sore throat

Long-Term Administration: The most frequent adverse reactions reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 Zovirax - treated patients were nausea (4 8%), diarrhea (2 4%), headache (1 9%) and rash (1 7%) The 589 control patients receiving intermittent treatment of recurrences with Zovirax for 1 year reported diarrhea (2 7%), nausea (2 4%), headache (2 2%) and rash (1 5%)

The most frequent adverse reactions reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1 5%), rash (1 3%) and paresthesia (0 8%) Reactions reported by 329 patients during the third year include asthenia (1 2%) paresthesia (1 2%) and headache (0 9%)

Herpes Zoster: The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral Zovirax 5 times daily for 7 to 10 days in 323 patients were malaise (11 5%), nausea (8 0%) headache (5 9%), vomiting (2 5%), diarrhea (1 5%) and constipation (0 9%) The 323 placebo recipients reported malaise (11 1%), nausea (11 5%) headache (11 1%), vomiting (2 5%), diarrhea (0 3%) and constipation (2 4%)

OVERDOSAGE: Precipitation of acyclovir in renal tubules may occur when the solubility (2 5 mg/mL) in the intratubular fluid is exceeded Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species rats treated with i v and i p doses of 20 mg/kg/day for 21 and 31 days, respectively and at s c doses of 100 mg/kg/day for 10 days, rabbits at s c and i v doses of 50 mg/kg/day for 13 days, and dogs at i v doses of 100 mg/kg/day for 31 days A 6 hr hemodialysis results in a 60% decrease in plasma acyclovir concentration Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION)

DOSAGE AND ADMINISTRATION: **Treatment of initial genital herpes**: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 10 days

Chronic suppressive therapy for recurrent disease: 400 mg (two 200 mg capsules or two teaspoonfuls [10 mL] suspension) 2 times daily for up to 12 months, followed by re-evaluation See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily

Intermittent Therapy: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 5 days Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules or four teaspoonfuls [20 mL] suspension) every 4 hours orally 5 times daily for 7 to 10 days

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications

Normal Dosage Regimen (5x daily)	Creatinine Clearance (mL/min/1 73m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval (hrs)
200 mg every 4 hours	> 10	200	every 4 hours 5x daily
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

For patients who require hemodialysis, the dosing schedule should be adjusted so that a dose is administered after each dialysis

References: 1. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection: a multicenter double-blind trial. *JAMA*. 1988;260:201-206. **2.** Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med*. 1988;85(suppl 2A):14-19. **3.** Data on file, Burroughs Wellcome Co., 1990.

IMPROVING LIVES THROUGH ANTIVIRAL RESEARCH

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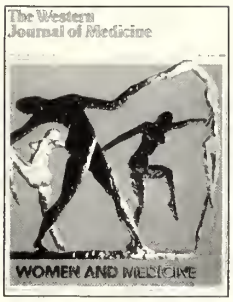
SPECIAL ISSUES

Addiction Medicine
and the Primary Care Physician

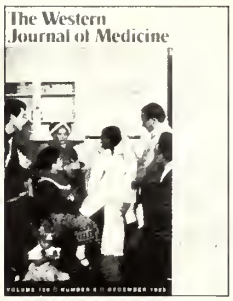
Addiction Medicine and the Primary Care Physician was conceived to be part of the initiative to expand the involvement of all specialties of medicine in the prevention and treatment of addictive disease. Topics covered include chemical dependence and the workplace, alcoholism, methadone maintenance in the treatment of opioid dependence, nicotine dependence, and treatment of cocaine dependence. David Smith MD, Special Editor, 1990.

Women and Medicine



This special issue explores both the professional side of women in medicine and the diagnosis and treatment of women patients. Topics covered include liver disease, women and AIDS, heart disease, hysterectomy, PMS, ovarian cancer, and women physicians and organized medicine. Linda Hawes Clever, MD, Special Issue Editor, 1988.

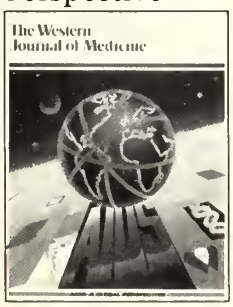
Cross-cultural Medicine



Cross-cultural medicine is devoted to the care of patients of different cultural, ethnic, or religious backgrounds. Subjects include Southeast Asian refugees in the American health care system, psychiatry and Chinese culture, health and illness in Filipino immigrants, and health care of Middle Eastern patients. M. Margaret Clark, PhD, Special Issue Editor, 1983. 2nd reprinted edition.

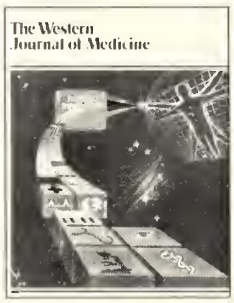
Also available:

AIDS—A Global Perspective



Jonathan M. Mann, MD
Special Issue Editor, 1987

Medical Informatics



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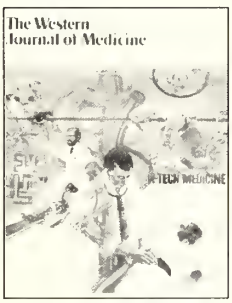
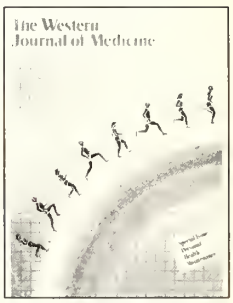
Special Issue Editor, 1986

High-Tech Medicine



R. Paul Robertson, MD
Special Issue Editor, 1985

Personal Health Maintenance



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ALASKA

The listing of continuing medical education programs in Alaska is supplied by the Alaska State Medical Association. To list programs, please send information to Alaska State Medical Association, 4107 Laurel St, Anchorage 99508; or phone (907) 562-2662.

April 24-27—**Alaska State Medical Association Annual Meeting.** Juneau. Wed-Sat. Contact: Alaska State Medical Association, 4107 Laurel St, Anchorage 99508. (907) 562-2662.

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

April 25-26—**Clinical Reviews 1991.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

April 27—**Gastroenterology: Update for the Family Practitioner.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Sat. Contact: Mayo-Clinic Scottsdale.

April 27—**Urology for the Primary Care Physician.** Mayo Clinic-Scottsdale at Scottsdale Plaza Resort, Scottsdale. Sat. Contact: Mayo Clinic-Scottsdale.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 16-19—**California Society of Anesthesiologists Annual Meeting.** CSA at Marriott Hotel, Anaheim. Thurs-Sun. 20 hrs. $175. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

September 7-8—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Horizon Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, Ste 410, Foster City. (800) 345-3691.

CARDIOLOGY

April 19-20—**Cardiac Diagnostic Methods and Risk Management.** Medical Education Resources at San Diego Hilton. Fri-Sat. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

April 22-May 1—**Cardiology for the Consultant: A Physician's Retreat.** Scripps Clinic and Research Foundation at Inn Rancho Santa Fe. 1½ wks. Contact: Mary Ann Morris, 860 SW Scherer Rd, Lee's Summit, MO 64063. (816) 524-5780.

June 21-22—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 1-3—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

August 2-4—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Hotel, Monterey. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 16-18—**Cardiac Diagnostic Methods and Risk Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051

(Continued on Page 394)

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(Continued from Page 392)

DERMATOLOGY

May 18-19—**Advanced Dermatologic Surgery Workshop.** UCLA at the Dermatologic Surgery Center, Los Angeles. Sat-Sun. 15 hrs. $800. Contact: UCLA.

July 11-14—**Advanced Seminars in Dermatology.** UCSF at Quail Valley Lodge, Carmel. Thurs-Sun. Contact: UCSF.

July 19-21—**Contact Dermatitis: The Basics.** Stanford at Hotel Meridien, San Francisco. Fri-Sun. Contact: Pamela Bain, Dept of Dermatology, Room R-122, Stanford 94305. (415) 723-7854.

August 16-20—**Fifth Annual Hot Spots in Dermatology: Masters Under the Mango Trees.** The Hawaii Dermatology Society and the Kauai Foundation at the Kaluakoi Hotel, Kepuhi Beach, Molokai, Hawaii. Fri-Tues. Contact: David Elpern, MD, Box 457, Kalaheo, HI 96741. (808) 245-1505.

EMERGENCY MEDICINE

May 6-10—**Postgraduate Institute for Primary Care and Emergency Physicians Symposium I: Cardiology, Pulmonary, Neurology.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. 32 hrs. $485. Contact: UCSD.

June 8-9—**Clinical Toxicology and Emergency Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $310. Contact: UCSF.

June 24-28—**Postgraduate Institute for Primary Care & Emergency Physicians Emergency Medicine Symposium III: Pediatrics, OB/GYN, Dermatology, Legal Aspects, Etc.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $260-$485. Contact: UCSD.

August 7-11—**Wilderness Medicine: '91.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Program Director, Box 321, Yreka 96097. (800) 888-5632.

August 19-23—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott, La Jolla. Mon-Fri. 32 hrs. $485. Contact: UCSD.

August 23-26—**Advances in Emergency Medicine.** Kaiser Permanente at Grand Hyatt Wailea Resort and Spa, Maui, Hawaii. Fri-Mon. Contact: Pat Salber, MD, Kaiser Permanente Hospital, 2200 O'Farrell, San Francisco 94115-3395.

FAMILY PRACTICE/PRIMARY CARE

April 26-28—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village, San Diego. Fri-Sun. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 26-28—**3rd Annual Clinical Strategies for the Primary Care Physician: Focus on Common Office Problems.** Santa Clara County Chapter of the American Academy of Family Physicians at Monterey Conference Center. Fri-Sun. 9 hrs. $155. Contact: SCAFP, PO Box 710184, San Jose 95171.

May 4—**Neurology for the Primary Care Physician.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sat. 5 hrs. $30. Contact: UCLA.

June 10-14—**UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

July 8-11—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

August 23-25—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

October 18-20—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

April 20—**Growth Factors in Clinical Medicine.** Scripps Clinic and Research Foundation at La Jolla. Sat. 4 hrs. $75. Contact: Laurie Jones, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

May 13-17—**Advances in Internal Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $585. Contact: UCSF.

May 25-27—**1991 CSIM Annual Meeting: Controversies, Challenges, Changes, and Calamari.** CSIM at Monterey Plaza Hotel. Sat-Mon. Contact: Cynthia Eaton, CSIM, Box 880606, San Francisco 94188-0606. (415) 882-5198.

June 15—**Lyme Disease Symposium.** Kaiser Permanente Northern California at El Rancho Tropicana Convention Center, Santa Rosa. Sat. 5 hrs. Contact: Joyce Appelbaum, 1950 Franklin, Oakland 94612. (415) 987-4726.

August 26-28—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

September 20-22—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sun. 18 hrs. $420. Contact: UCSF.

OB/GYN

April 18-20—**Advanced Pelviscopy and Endovaginal Sonography.** UCLA at Rancho Bernardo Inn, San Diego. Thurs-Sat. 19 hrs. $800. Contact: UCLA.

August 9-11—**4th Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: Memorial/UCI Center for Health Education, Box 1428, Long Beach 90801. (213) 595-3811.

August 16-18—**Office Gynecology for the Primary Care Physician.** San Diego State University at the Hyatt Islandia, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

OPHTHALMOLOGY

May 17-19—**California Association of Ophthalmology Annual Meeting.** CAO at Sheraton Grande Torrey Pines, La Jolla. Fri-Sun. Contact: Linda Xyz, (415) 777-3937.

PATHOLOGY

April 17-19—**12th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. $395. Contact: UCSF.

May 23-24—**Current Issues in Anatomic Pathology.** UCSF at Union Square Holiday Inn, San Francisco. Thurs-Fri. 12 hrs. $325. Contact: UCSF.

July 15-19—**Advances in Gastroenterology.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 19-22 hrs. $425. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 9-10—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684.

PEDIATRICS

April 18-19—**10th Annual Child Abuse.** UCD at Radisson Hotel, Sacramento. Thurs-Fri. Contact: UCD.

April 25-26—**10th Annual Conference on Child Abuse and Neglect.** UC Davis Medical Center at Radisson Hotel, Sacramento. Thurs-Fri. 12 hrs. $165. Contact: UCD.

May 16-18—**24th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 1—**Special Children: Pediatric Perspectives in the '90s.** Children's Hospital at Merritt Peralta Health Education Center, Oakland. Sat. 7 hrs. $150. Contact: Kim Leadon, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

June 21-23—**Current Concepts in Child Neurology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 15 hrs. Contact: Children's Hospital, (619) 576-4072.

August 19-21—**Pediatrics Update: 1991.** San Diego State University at the Hyatt Islandia, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

April 27-28—**The Cutting Edge: Being a Better Therapist.** UCSD at La Jolla Marriott, San Diego. Sat-Sun. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

(Continued on Page 396)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 394)

RADIOLOGY

April 21-26—**11th Annual San Diego Resident's Radiology Review Course.** UCSD at Hyatt Regency Hotel, La Jolla. Sun-Fri. 39 hrs. $435. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 27—**Introduction to Interventional Radiology.** UCSD at Hyatt Regency Hotel, La Jolla. Sat. 8 hrs. $100. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 18-21—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, Coronado. Thurs-Sun. 19.5 hrs. $400. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-24—**Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Wed. 14 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-27—**5th Annual MRI Symposium Including: Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Sat. 31 hrs. $695. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 25-28—**5th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 18 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

August 12-16—**Radiology for Clinicians.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 11-13—**The 7th Annual Sonography Update Conference and Exhibit.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 14-15—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 23-26—**Applied Ultrasound: Accent on Doppler.** University of Alabama at Birmingham at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 25-28—**Diagnosis of Musculoskeletal Disorders: State of the Art.** International Skeletal Society at Hotel del Coronado, San Diego. Wed-Sat. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

May 17-18—**What's New in Rehabilitation?** Memorial/UCI Center for Health Education at Queen Mary, Long Beach. Fri-Sat. Contact: UCI.

SURGERY

April 29-May 1—**11th Annual Scientific Meeting and Exhibition.** American Society for Laser Medicine and Surgery at the Sheraton on Harbor Island, San Diego. Mon-Wed. Contact: ASLMS, 2404 Stewart Square, Wassau, WI 54401. (715) 845-9283

May 2-4—**Advances in Knee Reconstruction Surgery: Ligament Reconstruction, Unicompartmental Replacement, and Patellofemoral Joint.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 26-hrs. $600. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 15-19—**13th Annual Wound Management Workshop: May.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $435. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

April 19-20—**HIV Update.** UCD at Holiday Inn Holidome, Sacramento. Fri-Sat. 12 hrs. Contact: UCD.

April 25-28—**Nevada State Medical Association Annual Meeting.** NSMA at Quail Lodge, Carmel. Thurs-Sun. Contact: Nevada State Medical Association, 3660 Baker Ln, Reno, NV 89502. (702) 825-6788.

May 23—**AIDS Update for Primary Care: Early Detection for Early Intervention.** Alta Bates-Herrick Hospital at Hospital Auditorium. Thurs. 7 hrs. $125. Contact: Mary Grim, (415) 540-1420.

June 28-30—**4th Annual Conference for the Medical Office Laboratory.** San Diego State University at Red Lion, San Diego. Fri-Sun. 18 hrs. $400. Contact: Anne Wright, (619) 594-6255.

(Continued on Page 398)

Specify Adjunctive

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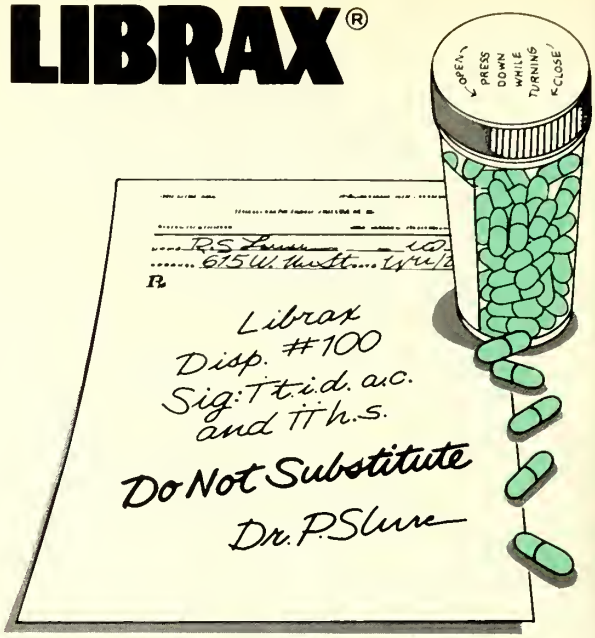

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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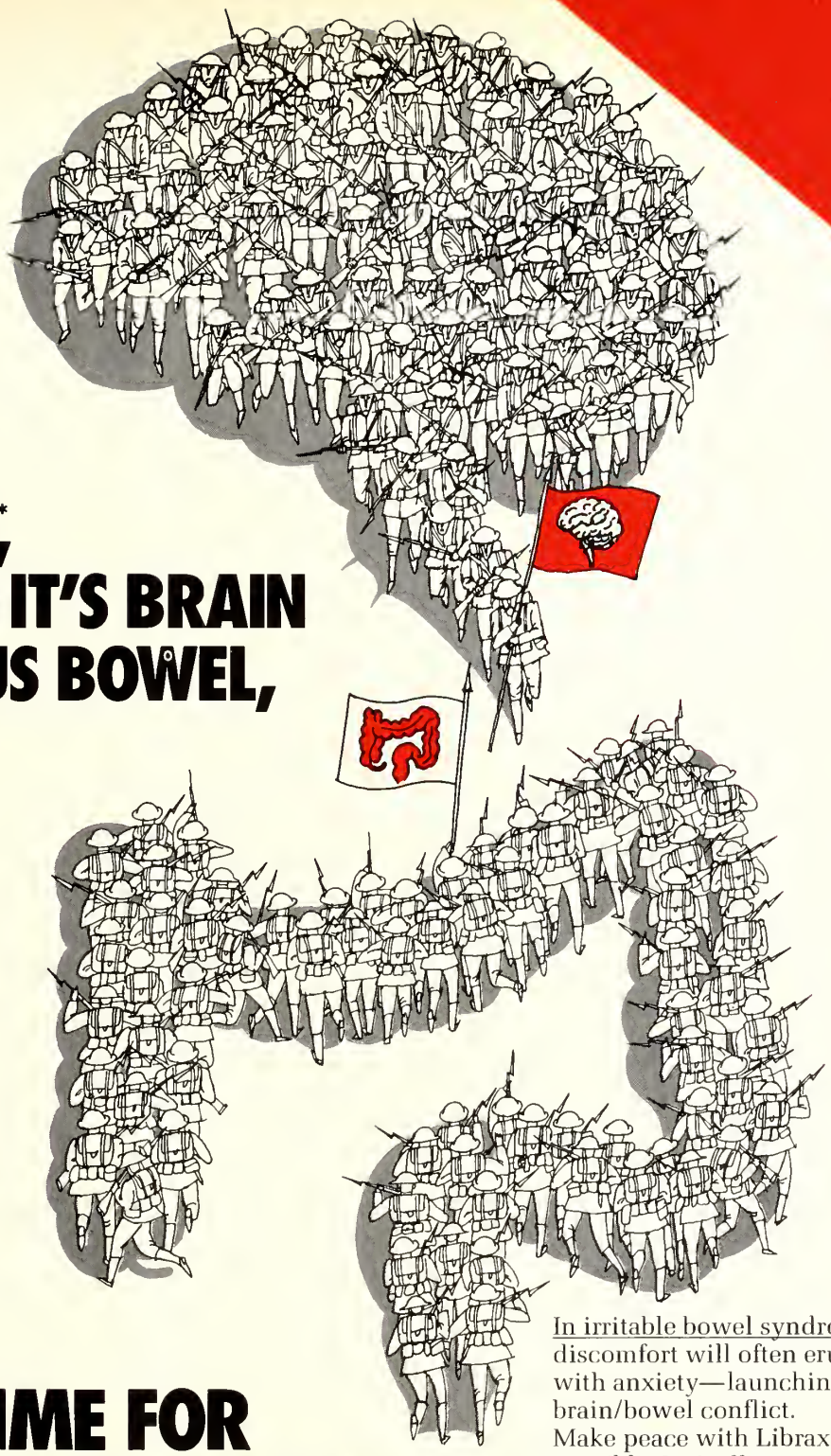

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Please see summary of prescribing information on adjacent page.

(Continued from Page 396)

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

April 15-19—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

April 25—**Perinatal Nursing Update.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

April 29-30—**Neonatal Resuscitation Instructor Course.** Children's Hospital, Denver. Mon-Tues. Contact: Pat Winter, (303) 861-6668.

June 7-8—**Fourth Annual Perinatal Summer in the Mountains Conference.** Children's Hospital of Denver at Glenwood Springs. Fri-Sat. Contact: Christine Sievers, (303) 861-6413.

June 25-27—**Community Health Traineeship.** Children's Hospital, Denver. Tues-Thurs. Contact: Christine Sievers, (303) 861-6413.

June 28-29—**Billings Perinatal Conference.** Children's Hospital of Denver at Billings, Montana. Fri-Sat. Contact: Christine Sievers, (303) 861-6413.

July 11—**Cultural Considerations in Perinatal Nursing.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

August 4-8—**34th Annual Pediatric Program.** University of Colorado School of Medicine, Children's Hospital, and the Colorado Chapter of the American Academy of Pediatrics at the Given Institute, Aspen. Sun-Thurs. Contact: Bobbi Rubingh, 1 (800) 882-9153 or (303) 270-5196.

August 5-9—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

August 8—**Basic and Advanced Fetal Heart Rate Monitoring.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

September 5, 12, 19, 26—**Comprehensive Perinatal Nursing Course.** University of Colorado Health Sciences Center. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

September 27-28—**Montrose Fall Clinics for Physicians.** Montrose Memorial Hospital, Montrose. Fri-Sat. Contact: Kathy Holman, (303) 240-7397.

October 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 7-10—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 14—**Preterm Infant Feeding Conference.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

November 22-23—**Colorado Springs Perinatal Conference.** Children's Hospital of Denver at Colorado Springs. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

December 2-6—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO (303) 270-5195.

IDAHO

April 25-28—**Comprehensive Review in Toxicology.** Idaho Poison Center, Boise. Thurs-Sun. 20 hrs. Contact: Dennis Emerson or Robin Clark, Idaho Poison Center, 1055 N Curtis Rd, Boise 83706. (208) 378-2159.

May 13-15—**Idaho Academy of Family Physicians—43rd Annual Meeting.** The Coeur d'Alene, Coeur D'Alene. Mon-Wed. Contact: Mrs Irma Sparks, Exec Dir, IAFP, PO Box 175, Boise 83701.

July 25-27—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 27—**Sleep Disorders Symposium.** Marriott Hotel, Albuquerque. Sat. Contact: Mary R. Boning, Presbyterian Healthcare Services, PO Box 26666, Albuquerque 87125. (505) 841-1225.

May 9-10—**New Mexico Medical Society Annual Meeting.** Albuquerque. Thurs-Fri. Contact: Glenn Taylor, NMMS, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or 1 (800) 748-1596.

May 10—**Molecular Biology of Disease: The Application of Modern Basic Science to Arteriosclerosis and Cancer.** The Marshall Building, Albuquerque. Fri. Contact: Glenn Taylor, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or 1 (800) 748-1596.

May 11—**Loss Control Seminar.** Holiday Inn Pyramid Hotel, Albuquerque. Sat. Contact: Diana E. Jaramillo, New Mexico Physicians Mutual Liability Company, PO Box 92890, Albuquerque 87199-2890. (505) 821-9485 or 1 (800) 432-0746.

June 8—**Transfusion Medicine: What's New in 1991.** Sheraton Old Town Hotel, Albuquerque. Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

August 5-9—**Body Imaging: Ultrasound, CT, MR, Nuclear Medicine.** El Dorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

(Continued on Page 400)

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(Continued from Page 398)

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

May 3-4—**Surgical Infections** (Sponsor: UUMC). Fri-Sat. University Park Hotel, Salt Lake City. Contact: (801) 581-8664.

May 10—**Ophthalmology, Annual Resident's Day, Clinical Conference** (Sponsor: UUMC). Fri. University of Utah, Salt Lake City. Contact: (801) 581-8664.

May 10-11—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

May 17—**Infectious Disease Update** (Sponsor: UUMC). Fri. Skaggs Hall Auditorium, University of Utah, Salt Lake City. Contact: (801) 581-8664.

May 30-31—**Communications Disorders** (Sponsor: UUMC). Thurs-Fri. Snowbird. Contact: (801) 581-8664.

June 9-11—**Interactive Video in Health Education—'Slice of Life'** (Sponsor: UUMC). Sun-Tues. University of Utah, Salt Lake City. Contact: (801) 581-8664.

June 17-21—**University of Utah School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Mon-Fri. University of Utah, Salt Lake City. Contact: (801) 581-8664.

July 8-13—**Update in Internal Medicine: Focus on Ambulatory Care Medicine** (Sponsor: UUMC). Sat-Thurs. Snowbird. Contact: (801) 581-8664.

July 12-14—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

September 27-29—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUMC:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 15-18—**The Best Approach 1991: Effective, Efficient Strategies in Cardiology, Orthopedics, Gastroenterology, and Pediatrics.** Kauai Sheraton, Hawaii. Fri-Mon. Contact: Group Health, (206) 326-3441.

April 15-26—**PM & R Review.** Seattle. Fri-Tues. Contact: U/W.

April 26-27—**Medical Issues of Active and Athletic Women.** Seattle. Fri-Sat. Contact: VMMC.

April 30-May 1—**AIDS Symposium: Pathogenesis of HIV Infection.** Spokane. Tues-Wed. Contact: WSU, (509) 335-2349.

May 1-3—**ACP: Clinical Topics in Pulmonary Medicine.** Seattle. Fri-Sat. Contact: VMMC.

May 9—**OB/GYN.** Everett. Thurs. Contact: (206) 258-6322.

May 10—**Office Procedures.** Tacoma. Fri. Contact: PCMS.

May 11—**Corneal Update.** Seattle. Sat. Contact: VMMC.

May 31—**Office Gynecology—1991.** Tacoma. Fri. Contact: PCMS.

June 1—**Substance Abuse.** Seattle. Sat. Contact: U/W.

June 7-8—**Topics in General Medicine.** Seattle. Fri-Sat. Contact: VMMC.

June 15—**Horizons in Urology.** Seattle. Sat. Contact: U/W.

June 24-25—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: VMMC, (206) 627-7137.

July 26-28—**Seafair XII: Regional Anesthesia.** Seattle. Fri-Sun. Contact: VMMC.

August 9-11—**International Conference on Pancreatic Cancer.** Seattle. Fri-Sun. Contact: VMMC.

September 12-13—**Resolving the Ethical Dilemmas in Animal Protocol Review.** Seattle. Thur-Fri. Contact: U/W.

September 26—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

December 6-7—**Urology.** Seattle. Fri-Sat. Contact: (206) 441-9762.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 13-15—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413. ◆

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In Memoriam

California Medical Association

Blackard, Embree, San Francisco. Died Jan 3, 1991, aged 61. Graduate of Duke University School of Medicine, Durham, North Carolina, 1953. Dr Blackard was a member of the San Francisco Medical Society.

Brown, James E., Vallejo. Died Feb 6, 1991, aged 56. Graduate of Stanford University School of Medicine, Stanford, California, 1966. Dr Brown was a member of the Solano County Medical Society.

Clark, Ira D., Los Gatos. Died Jan 19, 1991, aged 81. Graduate of Northwestern University Medical School, Chicago, Illinois, 1935. Licensed in California in 1950. Dr Clark was a member of the Santa Clara County Medical Association.

Crosley, Willard, Glendale. Died Nov 20, 1990, aged 79. Graduate of Case Western Reserve University School of Medicine, Cleveland, Ohio, 1940. Licensed in California in 1946. Dr Crosley was a member of the Los Angeles County Medical Association.

DiMichele, John D., Vacaville. Died Nov 17, 1990, aged 70. Graduate of University of Vermont College of Medicine, Burlington, 1945. Dr DiMichele was a member of the Solano County Medical Society.

Graham, Walter C., Santa Barbara. Died Nov 15, 1990, aged 84. Graduate of University of Nebraska College of Medicine, Omaha, 1934. Licensed in California in 1941. Dr Graham was a member of the Santa Barbara County Medical Society.

Huff, Elizabeth, Oakland. Died Feb 9, 1991, aged 83. Graduate of University of Chicago, Illinois, 1937. Dr Huff was a member of the Alameda-Contra Costa Medical Association.

Katz, Stanley, Los Angeles. Died Jan 11, 1991, aged 65. Graduate of University of Geneva, Switzerland, 1953. Licensed in California in 1979. Dr Katz was a member of the Los Angeles County Medical Association.

Mainwaring, George F., Oakland. Died Jan 5, 1991, aged 84. Graduate of Stanford University School of Medicine, Stanford, California, 1934. Dr Mainwaring was a member of the Alameda-Contra Costa Medical Association.

Michels, Leon, San Francisco. Died Dec 25, 1990, aged 81. Graduate of University of California, San Francisco, School of Medicine, 1934. Licensed in California in 1935. Dr Michels was a member of the San Francisco Medical Society.

Nelson, Theodore A., San Diego. Died Jan 1991, aged 70. Graduate of University of Kansas, Kansas City, 1948. Dr Nelson was a member of the San Diego County Medical Society.

Nixon, Norman, Laguna Beach. Died Nov 9, 1990, aged 91. Graduate of University of Iowa, Iowa City, 1925. Dr Nixon was a member of the Orange County Medical Association.

Phipps, Lewis E., Sacramento. Died Dec 16, 1990, aged 73. Graduate of University of California, San Francisco, 1951. Licensed in California in 1952. Dr Phipps was a member of the Sacramento-El Dorado Medical Society.

Pray, Laurence G., Palm Desert. Died Nov 14, 1990, aged 85. Graduate of Washington University School of Medicine, St Louis, Missouri, 1935. Licensed in California in 1969. Dr Pray was a member of the Riverside County Medical Association.

Reiner, Ralph, Fresno. Died Feb 2, 1991, aged 77. Graduate of University of California, San Francisco, School of Medicine, 1939. Licensed in California in 1939. Dr Reiner was a member of the Fresno-Madera Medical Society.

Sandler, Rodney Michael, Ukiah. Died Jan 25, 1991, aged 45. Graduate of Kings College Hospital Medical School, London, England, 1969. Dr Sandler was a member of the Mendocino-Lake County Medical Society.

Thompson, George N., Los Angeles. Died Jan 12, 1991, aged 81. Graduate of University of Southern California School of Medicine, Los Angeles, 1939. Licensed in California in 1939. Dr Thompson was a member of the Los Angeles County Medical Association.

Thorngate, George, Monterey. Died Jan 5, 1991, aged 97. Graduate of Case Western Reserve University School of Medicine, Cleveland, Ohio. Dr Thorngate was a member of the Monterey County Medical Society.

Tratar, Anton A., San Leandro. Died Dec 13, 1990, aged 68. Graduate of Marquette University School of Medicine, Milwaukee, 1946. Licensed in California in 1954. Dr Tratar was a member of the Alameda-Contra Costa Medical Association.

Walker, Pierre J., La Jolla. Died Oct 8, 1990, aged 96. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1923. Licensed in California in 1924. Dr Walker was a member of the Los Angeles County Medical Association.

Weeks, Carroll L., Hollywood. Died Nov 30, 1990, aged 84. Graduate of Stanford University School of Medicine, Stanford, California, 1933. Licensed in California in 1933. Dr Weeks was a member of the Los Angeles County Medical Association.

Weiss, Karl, Woodlake. Died Feb 8, 1991, aged 90. Graduate of University of California, San Francisco, School of Medicine, 1926. Dr Weiss was a member of the Tulare County Medical Society.

New Mexico Medical Society

Johnson, John J., Jr., Las Vegas. Died Jan 29, 1991, aged 86. Graduate of University of Tennessee College of Medicine, 1935. Licensed in New Mexico in 1936. Dr Johnson was a member of the San Miguel County Medical Society.

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Articles

Diagnosis and Antibiotic Treatment of Community-Acquired Pneumonia

JONATHAN E. RODNICK, MD, *and* JAMES K. GUDE, MD, *San Francisco, California*

Only a few pathogens cause most community-acquired pneumonias. In outpatients, treatment is empiric, based on the results of chest films, leukocyte counts, and Gram's stains (if available). Antibiotics must always cover pneumococci and should cover *Mycoplasma pneumoniae* in young adults and during epidemic periods. A follow-up chest film in smokers and those older than 40 years is strongly recommended. In inpatients, the evaluation and treatment are tailored to individual cases. A search for a wider range of causes, using invasive tests if necessary, is undertaken, and all likely pathogens should be covered with the initial antibiotic therapy.

(Rodnick JE, Gude JK: Diagnosis and antibiotic treatment of community-acquired pneumonia. West J Med 1991 Apr; 154:405-409)

Community-acquired pneumonia is an acute lower respiratory tract infection developing in nonhospitalized persons who have new focal findings on chest examination and an abnormal chest roentgenogram. It is estimated that in the United States each year, pneumonia develops in as many as 3 million persons, of whom about 500,000 are admitted to a hospital and about 50,000 die.[1] Assuming that there are about 150,000 physicians in primary care in this country—family practice, general internal medicine, and pediatrics—each full-time primary care physician could, conceivably, care for an average of 20 patients with pneumonia a year, of whom 2 to 5 might be admitted to a hospital. In more than 500,000 visits to family and general practitioners in Virginia, pneumonia was found to be the 25th most common problem seen and the reason for 0.8% of all the visits.[2] Although community-acquired pneumonia is a common office problem, there has been little published about its incidence in the United States and few controlled clinical trials of the treatment of it on an outpatient basis.

Etiology

Six recent studies have looked at the infectious causes of community-acquired pneumonia. Four of these were done on inpatients in the United Kingdom,[3] France,[4] Sweden,[5] and the United States.[6] Two studies were done on outpatients—in England[7] and Sweden.[8] Results of these studies are presented in Tables 1 and 2. The following generalizations are drawn:

- The spectrum of pathogens is similar for both inpatients and outpatients.
- *Streptococcus pneumoniae* is by far the most common cause in either setting. The percentage of patients with pneumococci in these reports may be underestimated. All studies tested for the pneumococcal antigen in sputum, which has a greater sensitivity but lower specificity than cultures.
- The incidence of infection with *Mycoplasma* and *Chlamydia* species may also be underestimated. *Mycoplasma pneumoniae* can be cultured, but more commonly it is diagnosed by a change in antibody titer, which can have false-negatives. None of these studies used sputum culture techniques for *Chlamydia* species, which are not routinely available. On the average, about 10% of cases of pneumonia in young adults are associated with *Chlamydia pneumoniae* (previously called the TWAR agent).[8]
- The incidence of viral pneumonia also may be underestimated. Percentages reported here are from positive sputum cultures or antibody titer rises due to influenza A and B only.
- All studies, despite using a wide spectrum of tests, were still not able to find the cause in a third of inpatient pneumonias and close to half of all outpatient pneumonias.

A probable order of frequency of the cause of community-acquired pneumonia in otherwise healthy young and middle-aged adults is *S pneumoniae, M pneumoniae, Haemophilus influenzae*, other causes of influenza, *C pneumoniae*, and *Branhamella catarrhalis. B catarrhalis* is a Neisseriaceae-like organism that is a seasonal pathogen, primarily causing pneumonia in those with underlying chronic lung disease.[10] In elderly, alcoholic, or debilitated patients, bacterial infections are more common, and pathogens such as *Mycobacterium tuberculosis*, the anaerobes, and gram-negative pathogens, as well as *Staphylococcus aureus*, must be considered—especially in times of influenza epidemics. Aspiration (anaerobic) pneumonia is usually seen in patients with major trauma, coma, stroke, or intoxication. In young children, *H influenzae* is a more common cause, but it still ranks after *S pneumoniae;* also, *S aureus* and respiratory syncytial virus are frequently seen in this age group.[11] Mycoplasmal and chlamydial infections and influenza occur in epidemics. Epidemics of *M pneumoniae* infection have been reported on a three- to seven-year cycle.[12] *M pneumoniae* is probably the most common cause of pneumonia in young adults but is rare in the elderly.[13]

In patients with the acquired immunodeficiency syndrome, the order of etiologic frequency (from most common to least common) of community-acquired pneumonia is *Pneumocystis carinii*, pyogenic bacteria (especially pneumococci), *Mycobacterium avium* complex, fungi (especially *Cryptococcus neoformans*), *M tuberculosis*, and cytomegalovirus. This ranking is based on data from Community Hospital of Sonoma County, Santa Rosa, California, where

From the Department of Family and Community Medicine, University of California, San Francisco, School of Medicine.
Reprint requests to Jonathan E. Rodnick, MD, Dept of Family and Community Medicine, UCSF School of Medicine, Box 0900, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
PPD = purified protein derivative

P carinii pneumonia was the most commonly diagnosed community-acquired pneumonia on the family practice-internal medicine service during the first six months of 1990.

Office Evaluation of Pneumonia

The signs and symptoms of pneumonia are well recognized. In the British Thoracic Society study of 453 patients with pneumonia, cough was present in 88%, dyspnea in 71%, sputum production in 69%, chest pain in 64%, hemoptysis in 17%, and confusion in 17%.[3] It is important to remember that pneumonia in the elderly can often present with confusion and a low-grade fever. Another not infrequent presentation of pneumonia in the very young and very old is upper quadrant abdominal pain, even with guarding and ileus. An upper respiratory tract infection precedes pneumonia only about a third of the time. Characteristic signs, symptoms, and findings of the two pneumonic "syndromes"—bacterial and atypical—are presented in Table 3. The rales and wheezes heard in the chest are nonspecific—they can also be heard in patients with bronchitis and those with congestive heart failure. The more specific signs, such as bronchial breath sounds, egophony, and dullness to percussion, are often heard later in the course, so may not help in the initial diagnosis. Normal findings on a chest examination exclude pneumonia 95% of the time.

For outpatients, only three diagnostic tests are used—a chest roentgenogram, leukocyte count, and Gram's stain of sputum specimens.

A chest x-ray film aids clinicians in three ways. First, it may help distinguish whether a pneumonia is bacterial or viral. Focal alveolar or lobar infiltrates on chest roentgenograms suggest bacterial infections. Diffuse interstitial infiltrates are suggestive of a viral, mycoplasmal, or chlamydial infection. Radiologists are able to distinguish bacterial from viral pneumonia correctly in more than two thirds of patients.[14]

Second, a chest film can determine if a pleural effusion is present. About a third of patients admitted to a hospital with pneumonia have a pleural effusion. If the effusion is small (it does not layer out to more than 2 cm on a lateral decubital film) and if a patient's condition does not appear toxic and responds well to antibiotic therapy, thoracentesis may not be needed. If, however, there is a larger effusion or if the infection is severe, thoracentesis is mandatory to exclude empyema.[15] The most common cause of empyema is an anaerobic infection; such an empyema occurs more frequently in patients with alcoholism or with impaired consciousness.

Third, follow-up chest films are needed to see if the infiltrate clears completely. More than 50% of chest films show pneumonia clearing within six weeks, and 75% show resolution within three months.[3] Follow-up films should be done within three to six months for all patients who smoke or who are older than 40. If an abnormality has not cleared on follow-up films, the patient should be evaluated for a possible cancer. In one study, half of patients with persistent abnormalities on follow-up chest films were found to have cancer.[12]

To help identify those patients who need hospital care, a leukocyte count should be done— <4 or $>30 \times 10^9$ per liter ($<4{,}000$ or $>30{,}000$ per μl). This also may aid in differentiating between pneumonia of viral or of bacterial cause. There is no clear dividing line between viral and bacterial pneumonias, although total counts of greater than 15×10^9 per liter (15,000 per μl) suggest a bacterial cause. The differential cell count is not a reliable indicator.

Last, if the patient has a productive cough, a Gram's stain should be done of sputum specimens. Patients with a productive cough are more likely to have a bacterial infection. A Gram's stain should be searched for areas where there are greater than 10 neutrophils per high-power field and few squamous epithelial cells, and the predominant bacteria in these areas should be identified. Unfortunately, a Gram's

TABLE 1.—*Causes of Community-Acquired Pneumonia in Patients Admitted to Hospital**

Study (Country), Year	Patients, No.	Streptococcus pneumoniae, %	Mycoplasma pneumoniae, %	Viral, %	Haemophilus influenzae, %	Staphylococcus aureus, %	Legionella Species, %	Chlamydia Species, %	Gram-negative, %†	Other, %	No Pathogen Identified, %
British Thoracic Society Research Committee (England), 1987[3]	453	42	18	7	6	1	2	3	2	3	33
Levy et al (France), 1988[4]	116	26	4	4	12	3	4	1	8	17‡	35
Holmberg (Sweden), 1987[5]	147	47	10	10	10	1	1	1	2	13	29
Fang et al (US), 1990[6]§	359	15	2	0	11	3	7	6	6	14	33

*Percentages will total >100% because some patients have more than one cause.
†Includes *Branhamella catarrhalis*.
‡Includes *Mycobacterium tuberculosis*.
§In the patients of Fang et al,[6] 3% had *Pneumocystis carinii* as the cause of their community-acquired pneumonia.

TABLE 2.—*Causes of Community-Acquired Pneumonia in Outpatients**

Study (Country), Year	Patients, No.	Streptococcus pneumoniae, %	Mycoplasma pneumoniae, %	Viral, %	Haemophilus influenzae, %	Staphylococcus aureus, %	Chlamydia Species, %	Gram-negative, %†	Other, %	No Pathogen Identified, %
Woodhead et al (England), 1987[7]	236	36	1	13	10	1	1	1	3	45
Berntsson et al (Sweden), 1986[8]	54	9	37	12	12	0	4	0	0	51

*Percentages will total >100% because some patients have more than one cause.
†Includes *Branhamella catarrhalis*.

stain has low sensitivity. For pneumococcal pneumonia, its sensitivity ranges from 15% to 60%.[16] When positive, however, it has a high predictive value of 80% to 90%.[3] Therefore, if a predominant organism is found, it is likely the cause of the pneumonia.

Because sputum is expectorated through the upper airway, which has many bacteria, sputum cultures are not usually helpful in patients with community-acquired pneumonia who are not admitted to a hospital. If the patient does not have a productive cough, no further diagnostic studies are warranted as an outpatient. The risks of doing a transtracheal aspirate generally outweigh the benefits.[17]

Evaluation in Hospital

Factors noted in the literature to be associated with increased mortality from pneumonia are presented in Table 4.[1,3,18,19] In patients with these risk factors, hospital admission should be strongly considered and a more detailed workup for the pathogens should be undertaken. The following tests should be considered:

TABLE 3.—*Characteristic Findings in Community-Acquired Pneumonia**

Characteristic	*'Typical Pneumonia'*	*'Atypical Pneumonia'*
Onset	Often sudden	Usually gradual
Myalgia, headache, photophobia	Not prominent	Often prominent
Rigors	Common	Rare
Toxicity	Marked	Mild to moderate
Cough	Productive, purulent, or bloody sputum	Nonproductive paroxysms or only scant mucoid sputum
Pleuritic pain	Common	Rare
Fever	>38.9°C (102°F)	<38.9°C (102°F)
Physical findings	Dullness with bronchial or tubular breath sounds	Often minimal
Roentgenographic findings	Localized; correlate with physical findings	Involvement in excess of physical findings
Leukocyte count	>15 × 10^9/liter†	<15 × 10^9/liter
Pathogen	Bacteria, *Legionella pneumophila*	*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, viruses

*Table courtesy of Mary Anne G. Johnson, MD, Dept of Family and Clinical Medicine, University of California, San Francisco.
†Leukopenia may be seen in overwhelming infection.

TABLE 4.—*Factors Associated With Increased Mortality From Pneumonia**

Advanced age
Male sex
Confusion
Underlying conditions, such as alcoholism, congestive heart failure, diabetes mellitus, cancer, or immunodeficiency (especially due to HIV)
Fever—temperature >38.3°C
Tachypnea—respiratory rate >30/minute
Hypotension—diastolic pressure <60 mm of mercury
Hypoxemia—O_2 saturation <88%
Leukopenia—<4 × 10^9/liter
Pronounced leukocytosis—>30 × 10^9/liter
Bacteremia
Bilateral or multilobe densities or large pleural effusion on chest film
Staphylococcal or gram-negative infection
Steroids, cytotoxic drugs, or other immunosuppressive therapy

HIV = human immunodeficiency virus

*From Fine et al,[1] the British Thoracic Society Research Committee,[3] Siegel,[18] and Marrie et al.[19]

• *Culture of two to three blood specimens.* Blood cultures are positive in 25% to 40% of patients with pneumococcal pneumonia.[3,4] Blood culture has lower sensitivity in other types of bacterial pneumonia.

• Legionella *culture or antibody titer.* Sputum culture for *Legionella pneumophila* is done with a selective medium and acid washing. Antibody titers can be measured only for *L pneumophila* serotype 1. An immunofluorescent titer of greater than 1:256 or a fourfold or greater rise in paired serum specimens is considered positive. Because of the time delay in getting culture or serologic results, the treatment of legionellosis, mycoplasmal or chlamydial infection, or viral pneumonia should usually be started on clinical suspicion.

• *Mycoplasmal titer.* Cold agglutinins are widely used but have low sensitivity and specificity, especially early in the course.[13] They are not advised. A fourfold rise in specific mycoplasmal complement fixation titers in paired serum specimens or a single immunoglobulin M titer of greater than 1:4 is diagnostic.

• *Chlamydial titers.* Unfortunately, no specific test or culture is available for *C pneumoniae.* Psittacosis or chlamydial pneumonia in newborns due to genital strains is diagnosed by a fourfold or greater rise in complement fixation or immunofluorescent titers or a single convalescent titer of greater than 1:64.

• *Viral culture or antibody titers.* Influenza virus types A and B can be cultured relatively easily. Alternatively, a fourfold rise in antibody titers is highly suggestive. Most laboratories will not look for the 180 or so other viruses capable of causing respiratory infections. The exception is respiratory syncytial virus, which causes bronchiolitis in children. The

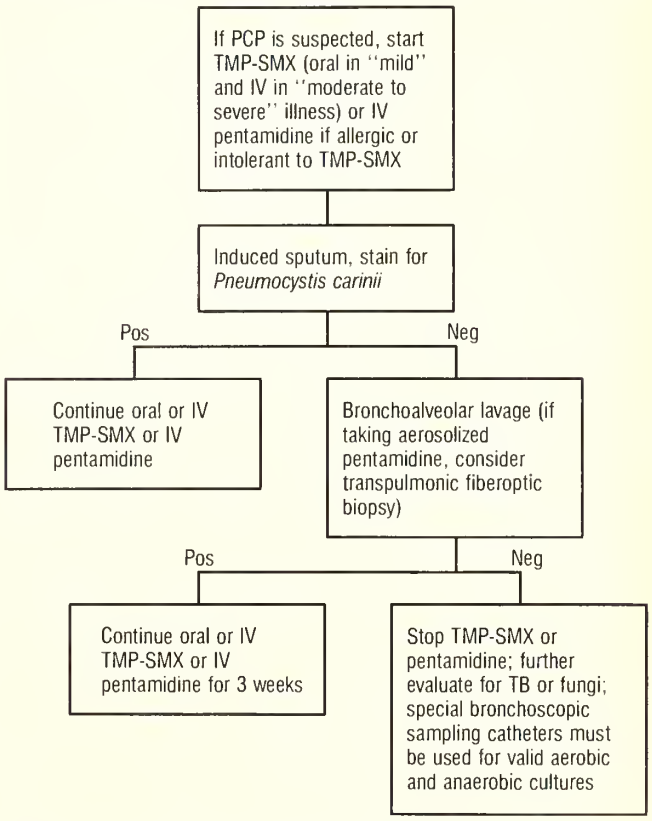

Figure 1.—The schema shows the approach to evaluating and treating suspected *Pneumocystis carinii* pneumonia (PCP) in patients positive for the human immunodeficiency virus antibody. IV = intravenous, TB = tuberculosis, TMP-SMX = trimethoprim and sulfamethoxazole

TABLE 5.—*Use of Gram's Stain of the Sputum to Select Initial Antibiotics for Outpatient Treatment of Pneumonia*

Gram's Stain Results	*Pneumonia Suspected*	*Initial Antibiotic Drug (Alternative)*
Few WBCs, no predominant organism	Viral or mycoplasmal or chlamydial	Erythromycin (tetracycline)
WBCs and gram-positive lancet-shaped diplococci	Pneumococcal	Penicillin (erythromycin)
WBCs and small gram-negative rods	*Hoemophilus influenzoe*	Amoxicillin; amoxicillin-clavulanate if β-lactamase strains prevalent
WBCs and large grape-like gram-positive cocci	Staphylococcal	Admit for IV nafcillin therapy (vancomycin)
WBCs and gram-negative rods	Gram-negative	Admit for IV aminoglycoside or cephalosporin therapy
WBCs and mixed pleomorphic flora	Unclear type	TMP-SMX and metronidazole or amoxicillin-clavulanate

IV = intravenous, TMP-SMX = trimethoprim and sulfamethoxazole, WBCs = leukocytes

enzyme-linked immunosorbent assay or immunofluorescent test for antigen in the sputum is also diagnostic.

• *Purified protein derivative (PPD) skin test and acid-fast bacilli (AFB) sputum smear.* A 5-TU (intermediate strength) PPD and sputum AFB smear and culture are recommended for patients with suggestive upper lobe infiltrates or other signs or symptoms suggesting tuberculosis.

• P carinii *smear.* Where indicated, an induced sputum specimen (sensitivity 20% to 50%) or, if normal, a bronchoalveolar lavage specimen (sensitivity 90%) should be examined for *P carinii.* The choice of stain depends on the laboratory's experience. Figure 1 outlines an approach to the evaluation of pneumonia in high-risk patients who are positive for human immunodeficiency virus antibodies.

• *Sputum bacterial culture.* This is often done more by habit than intention. If a patient is sick enough to be admitted to a hospital, however, a positive culture, despite its false-positives and false-negatives, may confirm a bacterial cause in those patients who have negative blood cultures, and the antibiotic sensitivities may be helpful. The culture results inspire more confidence if they correlate with a good Gram's stain.

• *Invasive diagnostic techniques.* Some invasive procedures, such as transbronchial needle biopsies, are used in sick patients who do not respond to empiric antibiotic therapy, but they yield a diagnosis only about 50% of the time.[17] A discussion of these techniques is beyond the scope of this article.

Treatment

Three questions must be answered. First, does a patient have pneumonia? This is usually determined by the results of a physical examination and chest roentgenogram. Second, should the patient be admitted to a hospital? This is addressed in the previous section. Third, what is the best antibiotic therapy to use?

If a patient is a "normal host," produces little or no sputum so a Gram's stain cannot be done, and is not being admitted to a hospital, the antibiotic drug of choice is erythromycin. The dosage for adults is 250 to 500 mg four times a day. Erythromycin covers pneumococci as well as *M pneumoniae* and *C pneumoniae.* Erythromycin frequently causes gastrointestinal side effects—nausea, vomiting, and diarrhea. These are dose related and are at least as common with the enteric-coated tablets as with the stearate or ethylsuccinate forms.[20] Even intravenous erythromycin causes gastrointestinal discomfort. In children, erythromycin estolate has a lower incidence of side effects, but its use should be avoided in adults because of the risk of cholestatic jaundice. Giving erythromycin with food or using small, frequent doses of a suspension may decrease the gastrointestinal side effects.

TABLE 6.—*Outpatient Drug Costs of Oral Antibiotics**

Drug, Dose, No.	*Cost, $*
Amoxicillin, 500 mg, 40	12.06
Amoxicillin-clavulanate potassium, 500 mg, 30	62.05
Ampicillin, 500 mg, 40	10.19
Cefaclor, 500 mg, 30	82.15
Cefixime, 400 mg, 10	45.26
Cefuroxime, 500 mg, 30	125.66
Ciprofloxacin hydrochloride, 750 mg, 20	84.35
Erythromycin, 500 mg, 40	13.76
Penicillin, 500 mg, 40	7.85
Trimethoprim-sulfamethoxazole, 160 mg-800 mg, 20	9.38

*Average retail costs in six community pharmacies, November 1989.

An alternative to erythromycin is tetracycline or doxycycline, but some pneumococci are resistant. Penicillin is not active against *Chlamydia* species or *M pneumoniae,* nor is ampicillin. The combination of trimethoprim and sulfamethoxazole provides adequate coverage for the three common bacterial pathogens—*S pneumoniae, H influenzae,* and *B catarrhalis*—but does not cover *M pneumoniae* or *C pneumoniae.* The newer and more expensive oral cephalosporins, such as cefaclor or cefuroxime, cover a similar respiratory pathogen spectrum as does trimethoprim-sulfamethoxazole. Ciprofloxacin has some activity against *M pneumoniae,* but high doses are needed to be bactericidal for pneumococci. It is not recommended as the initial drug of choice for respiratory tract infections.

If the patient is a "normal host" and produces a purulent sputum specimen, the sputum Gram's stain can help guide the antibiotic selection. The use of the Gram's stain for initial antibiotic selection is depicted in Table 5. If the Gram's stain shows pneumococci, an intramuscular injection of penicillin G procaine followed by penicillin V potassium, 500 mg four times a day (erythromycin or trimethoprim-sulfamethoxazole in penicillin-allergic patients), is an appropriate choice. If the Gram's stain suggests *H influenzae* or *B catarrhalis,* ampicillin, 500 mg four times a day, or amoxicillin, 500 mg three times a day, is a reasonable choice. If, however, the patient is from an area where β-lactamase-producing *H influenzae* is prevalent, a combination of amoxicillin and clavulanate potassium, 500 mg four times a day, is more appropriate. If the patient is allergic to penicillin, double-strength trimethoprim-sulfamethoxazole (160 mg and 800 mg) or an oral second- or third-generation cephalosporin (cefaclor, cefixime, or cefuroxime) has an effective antibacterial spectrum. The costs of a ten-day course of some typical oral antibiotic regimens are given in Table 6.

If a patient is admitted to hospital, the choice of antibiotic should obviously depend on the organism suspected. For a sick nursing-home patient or one with alcoholism in whom there is also concern about a gram-negative, anaerobic, or

staphylococcal infection, initial treatment with a parenteral combination drug, amoxicillin and sulbactam sodium, is a reasonable single-agent choice. If the primary concern is a staphylococcal infection, nafcillin or vancomycin is the agent of choice. If there is a possible pseudomonal infection (unusual in community-acquired pneumonia), gentamicin and ceftazidime are good initial choices. If the primary concern is anaerobic aspiration pneumonia, clindamycin is the best choice. In the case of an unclear cause where aspiration is a possibility, the use of trimethoprim-sulfamethoxazole and metronidazole or amoxicillin-clavulanate offers a wider initial empiric coverage.

The criteria for hospital discharge include the resolution of fever, an ability to take medicine orally, no need for supplemental oxygen, no progression of a chest film infiltrate, a decrease in the leukocyte count, and the presence of social and family support. Following the discharge of patients from a hospital, 75% return to normal activities within six weeks. The cost of treating an uncomplicated case of pneumonia in the hospital is in the range of $5,000, whereas treating a patient at home with oral antibiotics costs about $250 for physician visits, chest roentgenograms, and antibiotics. The diagnosis-related group 089 for uncomplicated pneumonia was based on allowing 7½ days of hospital treatment.

Prevention

The influenza vaccine is protective at a 70% to 80% level for the current covered strains. (The 1990-1991 vaccine included A/Taiwan, A/Shanghai, and B/Yamagata hemagglutinin antigen.) Unfortunately, less than 20% of patients older than 65 or others at high risk (residents of long-term-care facilities or those with chronic cardiac, renal, or hematologic illness) are immunized each year. If an actual influenza outbreak is relatively certain, amantadine is also 70% to 90% protective.[21] The usual dose is 200 mg a day, but in the elderly, 100 mg a day is recommended to decrease the side effects of insomnia, dizziness, and personality changes. The use of the pneumococcal vaccine is more controversial. It probably reduces the chances of pneumococcal pneumonia by 60% to 80% in healthy elderly persons, but this may be lower in those with underlying conditions.[22] The pneumococcal vaccine is recommended for any adult with a chronic illness. Last, a recent recommendation is to give the Haemophilus b vaccine to children beginning at 2 months to protect against meningitis. This vaccine is unlikely to do much to decrease the incidence of *H influenzae* respiratory infections, however, because pneumonia is usually caused by nontypeable serotypes.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the Special Editors.

STEPHEN M. McPHEE, MD
TERRIE MENDELSON, MD
Special Editors

Articles

Thrombotic Thrombocytopenic Purpura Treated With Plasma Exchange or Exchange Transfusions

KIRK V. SHEPARD, MD; ANDREW FISHLEDER, MD; FRED V. LUCAS, MD; MARLENE GOORMASTIC, MPH; *and* RONALD M. BUKOWSKI, MD, *Cleveland, Ohio*

Of 40 patients with thrombotic thrombocytopenic purpura, 17 were treated with plasma exchange, 15 with exchange transfusions, and 6 with both types of therapy. One patient died before being treated and another patient was seen but not treated. Plasma exchange was performed daily for a mean of seven exchanges per patient. The replacement fluid during plasma exchange was fresh frozen plasma in all cases. The complete response rates for each type of treatment were as follows: 88% for plasma exchange (15 patients), 47% for exchange transfusions (7 patients), and 67% for exchange transfusions and plasma exchange (4 patients). Clinical and laboratory factors were examined for any statistically significant association with therapy response. Treatment with plasma exchange was statistically the initial factor most strongly associated with prognosis. Paresis, paresthesias, seizures, mental status change, and coma showed no association with response to treatment. Some of the laboratory factors that did not show significant association with treatment response were the initial creatinine, hemoglobin, platelet count, lactate dehydrogenase, and total bilirubin. This study supports the hypothesis that plasma exchange has significantly improved the prognosis of patients with thrombotic thrombocytopenic purpura. These patients should be treated aggressively regardless of the severity of their symptoms.

(Shepard KV, Fishleder A, Lucas FV, Goormastic M, Bukowski RM: Thrombotic thrombocytopenic purpura treated with plasma exchange or exchange transfusions. West J Med 1991 Apr; 154:410-413)

Thrombotic thrombocytopenic purpura (TTP) is a rare syndrome of unknown etiology that is characterized by the clinical picture of a microangiopathic hemolytic anemia, thrombocytopenia, neurologic symptoms, renal disease, and fever. The disease was first described by Moschcowitz in 1925.[1] In 1964, Amorosi and Ultmann reviewed 271 cases of TTP and reported a 90% mortality rate in these patients regardless of their treatment.[2] Ridolfi and Bell reviewed another 275 cases of TTP reported from 1964 to 1980.[3] In these patients, treatment with corticosteroids, blood or plasma exchange, plasma infusion, antiplatelet agents, or splenectomy resulted in a 46% survival rate.

The pathogenesis of TTP is poorly understood. On histologic study, TTP is characterized by the presence of intravascular hyaline thrombi composed mainly of platelets with some fibrin in the arterioles and capillaries.[4] Many treatment regimens have been employed with varying success, including splenectomy, corticosteroids, antiplatelet agents, heparin, whole blood exchange transfusions, hemodialysis, plasma infusions, vincristine, and plasma exchange.[5-18] Due to the rarity of this disorder, clinical studies of the treatment of TTP usually include only a few patients. The literature is particularly devoid of clinical reports studying plasma exchange and exchange transfusions in the treatment of TTP in large numbers of patients. Although certain initial clinical findings indicate a poor prognosis in the natural history of patients with TTP, it is important to study these same clinical findings to determine if they are still prognostically important in the face of the modern therapy for this disease.[19,20]

At the Cleveland Clinic Foundation interest in TTP and its treatment with exchange transfusions first developed more than two decades ago when patients were first treated successfully by this method.[12] In the 1970s we reported the successful treatment of a series of patients with TTP with plasma exchange.[17] The purpose of this report is to review our updated clinical experience with the treatment of TTP with plasma exchange or exchange transfusions and to study any factors that may be important in predicting the treatment outcome.

Patients and Methods

We reviewed the medical records of all patients admitted to the Cleveland Clinic Foundation with the diagnosis of TTP between 1960 and 1986. The diagnosis was considered consistent with the classic picture of TTP if defined by five clinical findings: microangiopathic hemolytic anemia, thrombocytopenia, renal abnormalities, fever, and neurologic changes. Microangiopathic hemolytic anemia and thrombocytopenia had to be present with at least one of the other three clinical findings. Four patients were excluded because their records showed insufficient criteria for the definition of TTP. In all, 23 (58%) were women. Of the 40 patients, 30 were white, 9 were African American, and 1 was Native American.

Of the 40 patients, 17 were treated with plasma exchange alone. The initial frequency of plasma exchange was once a day except for one patient who received plasma exchange every other day. The procedure was done using the Aminco continuous-flow blood cell separator through catheters placed in the antecubital veins. During each treatment, 5,000 units of heparin was administered. In all the patients, 2 to 3 liters of plasma was exchanged for fresh frozen ABO- and

From the Departments of Medicine (Dr Shepard), Experimental Therapeutics (Dr Bukowski), Laboratory Hematology (Drs Fishleder and Lucas), and Biostatistics (Ms Goormastic), The Cleveland Clinic Foundation, Cleveland, Ohio.

Reprint requests to Ronald M. Bukowski, MD, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195.

ABBREVIATIONS USED IN TEXT

SD = standard deviation
TTP = thrombotic thrombocytopenic purpura

Rh-compatible plasma. The mean number of total exchanges per patient was 6.8 ± 3.7 standard deviations (SD) (range, 3 to 21). The procedure required two to three hours to exchange the desired amount of plasma. The mean number of total liters exchanged per patient was 18.2 ± 16.1 SD (range, 4.3 to 64.9).

Of the 40 patients, 15 were treated with exchange transfusions alone by the following method: The skin overlying the femoral vein was prepared with benzalkonium chloride and thimerosal. The skin was then infiltrated with 1% lidocaine, and a small incision was made. An 18-gauge Seldinger needle was inserted into the vein, the stylet removed, and the guide wire directed into the inferior vena cava. A Sheldon cannula was then advanced over the wire and into the vein with subsequent removal of the wire. A second Sheldon catheter was then placed in the same vein by a similar technique. Donor blood was then collected in acid-citrate-dextrose solution and used within three hours.

A unit of fresh whole blood was infused through one catheter. When the infusion was completed, a unit of blood was removed through the other cannula. The blood was then alternately infused and removed in this manner until the desired number of units had been exchanged. A transfusion pressure pump and vacuum bottle were used to facilitate the procedure. After every fourth unit transfused, 10 ml of a solution of 10% calcium gluconate was administered intravenously. Patients' vital signs and electrocardiograms were monitored during the exchange. The total time usually required for completion of the exchange transfusion was two to three hours. The number of units exchanged varied from 8 to 12 units.

Six patients were treated with exchange transfusions and then, when they failed to respond, plasma exchange. One patient died before being treated, and one patient was seen but not treated. None of the patients received aspirin as treatment of their TTP, but 7 patients received dipyridamole and 24 patients received corticosteroids at some time during their treatment course. Only one patient had a splenectomy with no therapeutic response before being successfully treated with exchange transfusions.

A complete response to therapy was defined as the resolution of the following indices after treatment with plasma exchange or exchange transfusions for at least three months: an increase of the platelets to more than 150 × 10^9 per liter (150,000 per μl), a normal peripheral blood smear, and normal results on neurologic examination. To be eligible for

TABLE 1.—*Physical and Historical Findings of 40 Patients With Thrombotic Thrombocytopenic Purpura*

Physical and Historical Findings	*Patients, No. (%)*
Mental status change	25 (63)
Malaise	24 (60)
Fever	22 (55)
Ecchymoses	22 (55)
Headache	20 (50)
Petechiae	19 (48)
Neurologic focal deficits	15 (38)
Jaundice	13 (33)
Coma	13 (33)
Abdominal pain	13 (33)
Nausea	12 (30)
Paresis	11 (28)
Paresthesias	10 (25)
Seizures	10 (25)
Dysarthria	9 (23)
Vision changes	6 (15)
Aphasia	5 (13)
Splenomegaly	1 (3)

TABLE 2.—*Association of Clinical Variables With Treatment Response**

Variable	*Complete Responders, %*	*Non-responders, %*	*P Value†*
Petechiae			
Yes	38	73	.08
No	62	27	
Nausea			
Yes	40	18	.27
No	60	82	
Neurologic focal deficits	31	55	.27
Abdominal pain			
Yes	38	18	.28
No	62	82	
Seizures			
Yes	23	36	.44
No	77	64	
Coma			
Yes	27	45	.44
No	73	55	
Jaundice			
Yes	31	50	.44
No	69	50	
Paresis			
Yes	36	20	.45
No	64	80	
Headache			
Yes	62	45	.47
No	38	55	
Ecchymoses			
Yes	54	73	.47
No	46	27	
Race (white)			
Yes	73	82	.57
No	27	18	
Fever			
Yes	54	55	.63
No	46	45	
Dysarthria			
Yes	29	18	.69
No	71	82	
Paresthesias			
Yes	25	36	.69
No	75	64	
Mental status change			
Yes	62	73	.71
No	38	27	
Malaise			
Yes	62	70	.72
No	38	30	
Gender			
Male	38	45	.73
Female	62	55	
Splenomegaly			
Yes	4	0	.99
No	96	100	
Vision changes			
Yes	17	9	.99
No	83	91	
Aphasia			
Yes	17	9	.99
No	83	91	

*26 patients had a complete response, and 12 had no response to treatment. Information on some of the variables was absent for some patients.

†As determined by Fisher's exact test.

evaluation of response, patients had to be observed for at least three months after therapy. A Fisher's exact test was used for categoric variables. Because many of the continuous factors of interest have extreme values or have abnormal distributions, a nonparametric test (Wilcoxon rank sum test) was used to test for location differences between the complete responders and the nonresponders.

Results

Many of the demographic and clinical factors listed in Table 1 were studied for any statistically significant association with treatment response. None of the factors analyzed from the patients' characteristics, history, or physical findings were associated with a response or lack of response to therapy (Table 2). Table 3 lists the initial laboratory data available at the time of a patient's presentation. Of these factors, only an elevated initial leukocyte count was significantly associated with a good treatment response (Table 4).

Of 17 patients treated with only plasma exchange whose treatment response was evaluated, 15 (88%) had a complete response; of 15 patients treated with only exchange transfusions, 7 (47%) had a complete response; and of 6 patients treated with both exchange transfusions and plasma exchange, 4 (67%) had a complete response.

When the treatment modalities were compared, the presence of plasma exchange in the therapy regimen was a statistically significant factor predicting a complete response ($P = .03$) (Table 5). Treatment with plasma exchange alone or in combination with exchange transfusions produced a higher response rate than did exchange transfusions alone ($P = .04$). At some time during their clinical course, 24 patients were given corticosteroids, but no significant difference was noted in treatment response rates between patients who received corticosteroids and those who did not ($P = .68$). Only seven patients were given dipyridamole at some time during their clinical course, and the addition of these antiplatelet agents did not appear to make a difference in the treatment response.

TABLE 3.—*Initial Pretreatment Laboratory Data of Patients With Thrombotic Thrombocytopenic Purpura*

Test	Patients, No.*	Median	Reference Interval
Blood tests			
Leukocytes × 10^9/liter	39	9.8	5 to 11
Hemoglobin, grams/liter	39	88	125 to 160
Lactate dehydrogenase, U/liter	34	1,358	100 to 185
Total bilirubin, mg/dl†	38	2.7	0.3 to 1.0
Creatinine, mg/dl†	34	1.5	1.4
Blood urea nitrogen, mg/dl†	37	29	10 to 20
Fibrinogen, grams/liter	26	2.9	2.0 to 4.0
Prothrombin time, seconds	35	13	10 to 13
APTT, seconds	26	25.5	21 to 31
Platelets × 10^9/liter	39	20.5	150 to 400
Urine protein (dipstick)			
Negative	8		
Trace +	14		
1 to 2 +	9		
3 to 4 +	3		
Urine sediment			
Normal	8		
Abnormal	28		

APTT = activated partial thromboplastin time

*Not all values are available for each patient.

†Values are given in conventional units. To convert to Système International (SI) units, the conversion factor for total bilirubin is 17.10 (to μmol per liter), for creatinine is 88.40 (to μmol per liter), and for blood urea nitrogen is 0.357 (to mmol per liter of urea)

With the mean follow-up time of the responders being 5.2 years as of June 1, 1987, three patients have had relapses of TTP after successful treatment at the Cleveland Clinic Foundation. Two of the patients originally had been treated with plasma exchange and exchange transfusions and the other patient with plasma exchange and splenectomy. The relapses occurred at two years after treatment in one patient and at one and nine years after treatment in another patient. The third patient has had six relapses 1½ years to 8 years after initial treatment. All patients' relapses were treated successfully.

Discussion

For four decades after the initial description of thrombotic thrombocytopenic purpura by Moschcowitz in 1925, this unusual syndrome led to death in almost all cases.[2] Although some patients with TTP had a more prolonged clinical course (chronic TTP), the vast majority of cases showed an acute course sometimes leading to death in hours or days. Some of the early therapeutic efforts included splenectomy and the use of corticosteroids and heparin.[5,6,11] The use of antiplatelet agents such as aspirin, dipyridamole, or dextran has met with varying success.[7-10]

The first breakthrough in the treatment of TTP was the use of whole blood exchange transfusions. This method of treatment was first attempted by Rubinstein and colleagues,[21] and the patient recovered. Bukowski and co-workers reported the cases of 13 patients who were treated with exchange transfusions, 7 of whom had remissions.[12] This re-

TABLE 4.—*Median Initial Laboratory Values Associated With Therapeutic Outcome*

Variable	Complete Responders (n=26) Median	Non-responders (n=12) Median	P Value*
Leukocytes × 10^9/liter	11.9	6.8	.05
Hemoglobin, grams/liter	96	72	.15
Blood urea nitrogen, mg/dl†	31	26	.40
Prothrombin time, seconds	13	14	.44
Age, yr	37	49	.49
Lactate dehydrogenase, U/liter	1,358	1,750	.59
Total bilirubin, mg/dl†	2.8	2.9	.69
Fibrinogen, grams/liter	2.9	3.0	.75
Creatinine, mg/dl†	1.3	1.5	.91
Platelets × 10^9/liter	20	20.5	.80

*As determined by the Wilcoxon rank sum test.

†Values are given in conventional units. See Table 3 for conversion factors to Système International units.

TABLE 5.—*Association of Treatment Method With Therapeutic Response*

Treatment	Complete Responders, No.	(%)	Non-responders, No.	(%)	P Value*
Plasma exchange					
Yes	19	(73)	4	(33)	.03
No	7	(27)	8	(67)	
Exchange transfusion					
Yes	11	(42)	10	(83)	.03
No	15	(58)	2	(17)	
Plasma exchange alone	15	(58)	2	(17)	.04
Exchange transfusion alone	7	(27)	8	(67)	
Both	4	(15)	2	(17)	

*As determined by Fisher's exact test.

port was followed by that of Pisciotta and associates, which confirmed that about 50% of patients with TTP could survive when treated with exchange transfusions.[22]

As plasma exchange technology was developed, it was successfully applied in the management of patients with TTP.[17] Although this technique has been studied alone and in combination with a variety of other therapies—such as corticosteroids, hemodialysis, splenectomy, antiplatelet agents, and vincristine—most of these clinical series have had a small number of patients, usually fewer than ten.[9,16-20] One problem with small clinical series that have used the multiagent approach in treating TTP is that the interpretation of results is difficult. The multiagent approach has been successful in many clinical series, but it offers no clear answers regarding which treatment methods are most important.

This report of patients with TTP treated at the Cleveland Clinic Foundation represents the largest number of patients treated with plasma exchange or exchange transfusions at a single institution. It therefore presents a group of patients treated in a relatively uniform manner, and it allows the efficacy of plasma exchange and exchange transfusion to be studied. Thus, the prognostic factors that may predict treatment outcome can be more precisely analyzed.

Thrombotic thrombocytopenic purpura can no longer be regarded as fatal in most patients; plasma exchange successfully treated 88% of the patients in our study. Of the patients treated with exchange transfusions alone, 47% had complete responses. This figure is consistent with other studies[17,20,22] in which approximately half of the patients had complete responses when treated in this manner. A direct comparison of the two methods must be made with caution, however, because the majority of patients treated before 1975 were treated with exchange transfusions.

The mechanism underlying the therapeutic success of different treatment methods remains speculative, in part because many clinical series have a multiagent approach to treating TTP. It may be that the effects of plasma exchange and whole blood exchange transfusions are related to the removal of a soluble toxic material.[4,23] Alternatively, the addition of a deficient "plasma factor" or a dilutional effect by the transfusion of whole blood or plasma in plasma exchange may be the crucial factor in the successful treatment of TTP.[24,25]

In this study, the strongest therapeutic factor associated with prognosis was treatment with plasma exchange. An elevated initial leukocyte count was the only laboratory factor that showed a significant association with response. Most important, no clinical findings predicted a poor response to treatment. Neither age nor gender was predictive. Patients with severe symptoms, such as the presence of seizures, paresthesias, paresis, aphasia, mental status changes, or coma, did as well as patients with milder symptoms. This is contrary to other clinical studies, in which it was found that patients with certain clinical factors did less well than other patients with TTP.[19,20] The results from our study emphasize that the treatment of a patient with severe neurologic symptoms can be as successful as the treatment of less symptomatic patients if aggressive treatment with plasma exchange or exchange transfusions is instituted.

Treatment with plasma exchange has substantially improved the prognosis of patients with TTP. There are no clearly prognostic clinical findings, and even patients with severe initial clinical findings may respond well to aggressive treatment. The mechanism of the benefit of plasma exchange remains speculative, as does the question of whether additional therapeutic modalities will improve an 88% rate of response to plasma exchange.

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Articles

Access to Medical Care for Documented and Undocumented Latinos in a Southern California County

F. ALLAN HUBBELL, MD, MSPH; HOWARD WAITZKIN, MD, PhD; SHIRAZ I. MISHRA, MD; JOHN DOMBRINK, PhD; *and* LEO R. CHAVEZ, PhD, *Irvine, California*

To determine local access to medical care among Latinos, we conducted telephone interviews with residents of Orange County, California. The survey replicated on a local level the national access surveys sponsored by the Robert Wood Johnson Foundation. We compared access among Latino citizens of the United States (including permanent legal residents), undocumented Latinos, and Anglos, and analyzed predictors of access.

Among the sample of 958 respondents were 137 Latino citizens, 54 undocumented Latinos, and 680 Anglos. Compared with Anglos, Latino citizens and undocumented immigrants had less access to medical care by all measures used in the survey. Although undocumented Latinos were less likely than Latino citizens to have health insurance, by most other measures their access did not differ significantly. By multivariate analysis, health insurance status and not ethnicity was the most important predictor of access. Because access to medical care is limited for both Latino citizens and undocumented immigrants, policy proposals to improve access for Latinos should consider current barriers faced by these groups and local differences in access to medical care.

(Hubbell FA, Waitzkin H, Mishra SI, Dombrink J, Chavez LR: Access to medical care for documented and undocumented Latinos in a southern California county. West J Med 1991 Apr; 154:414-417)

Latinos—Mexican Americans, Mexican nationals, and other persons of Latino descent—face major barriers to access to medical care in the United States. Latinos are less likely than any other ethnic group to have health insurance. In a recent national survey,[1] Latinos were more than twice as likely as African Americans and nearly three times as likely as Anglos to lack health insurance. Latinos in that survey also reported deficiencies in other important measures of access, such as having a regular source of health care or having at least one ambulatory office visit during the previous year.

These findings are disturbing not only because of the potential effects on the health of this population but also because Latinos are the fastest growing minority in the United States.[2] Since 1980, the number of Latinos in the United States has risen by 39%, five times the growth rate of all other ethnic groups. The 20.1 million Latinos now living in the United States make up 8.2% of the population.

Although nearly a third of all US Latinos live in California, little reliable information exists about their access to medical care. As part of a community-oriented needs assessment, we studied access to medical care for Latinos in Orange County, an urban community in southern California. In 1989, Latinos accounted for approximately 23% of the county's more than 2 million residents.[2] Moreover, an estimated 150,000 undocumented persons live in the county. Thus, Orange County provides a good setting to study access in this important minority group.

We report herein a comparison of access measures among Latino citizens, undocumented Latinos, and Anglos; an analysis of the predictors of access among Latinos; and a discussion of the health policy implications of the findings.

Methods

During October 1987 and February 1988, we conducted telephone surveys of residents in the northern inland portion of Orange County, an area where many Latinos live, to determine access to medical care. A detailed description of our methods appeared in a previous report.[3] In the October survey, we contacted 652 families—300 families with incomes less than 125% of the national poverty level (which we classified as "poor") and 352 families with incomes between 125% and 200% of that level (which we described as "nearly poor"). The national poverty level at the time of the survey was $11,200 per year for a family of four. We chose these low-income families randomly from census tracts in which at least 100 households had incomes below the national poverty level (according to 1980 US census data). In the February survey, we contacted a group of 306 families with incomes greater than 200% of the national poverty level (which we classified as "nonpoor"). We selected these families from a random sample of telephone numbers of families living in the same geographic location as the low-income group.

Our survey instrument was designed to replicate on a local level previous national surveys on access to medical care supported by the Robert Wood Johnson Foundation.[1] The questionnaire consisted of closed- and open-ended questions that focused on demographic characteristics, access to care, and health status. We classified all respondents who identified their ethnicity as Mexican, Chicano, or Latino as Latino for the purposes of this study. Another demographic characteristic of interest was immigration status. Because of the sensitive nature of this question, we asked it at the end of the survey after reassuring respondents that their answers

From the Department of Medicine (Drs Hubbell and Waitzkin), the Program in Social Ecology (Drs Hubbell, Mishra, and Dombrink), the Department of Anthropology (Dr Chavez), and the Public Policy Research Organization (all authors), University of California, Irvine.

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Reprint requests to F. Allan Hubbell, MD, MSPH, Department of Medicine, UCI Medical Center, 101 City Drive, Orange, CA 92668.

TABLE 1.—*Demographic Characteristics of Latino and Anglo Adults**

Characteristic	Latino All (n=191), %	Latino Undocumented (n=54), %	Latino Citizen (n=137), %	Anglo (n=680), %
Age, yrs				
<40	65	87†	56‡	36
40-65	29	11	36	29
>65	6	2	8	34
Sex				
Male	33	46†	28	30
Female	67	54	72	70
Income§				
Poor	65	81†	59‡	21
Nearly poor	26	17	29	40
Nonpoor	9	2	12	38
Employment Status				
Employed	58	74†	52	47
Unemployed	11	8	12	8
Not in the work force (homemaker, retired, student)	31	18	36	45

*Percentages are of valid responses. Not all totals equal 100% because of rounding error.

†$P<.01$, which is the difference in frequency of a demographic characteristic between Latino citizens and undocumented Latinos by 2-tailed χ^2 testing.

‡$P<.01$, which is the difference in frequency of a demographic characteristic between Latino citizens and Anglos by 2-tailed χ^2 testing.

§"Poor" refers to families with incomes less than 125% of the national poverty level ($11,200/yr for a family of 4), "nearly poor" were those with incomes between 125% and 200% of that level, and "nonpoor" were those with incomes more than 200% of that level.

would remain confidential. The questionnaire segment on access contained questions about health insurance status, regular source of care, physician visits within the past year, and barriers to care. For purposes of the survey, respondents possessed health insurance if they had any private or government-sponsored health insurance, including Medicare, Medi-Cal (California's equivalent to Medicaid), and the county's indigent medical services program. The segment on health status included questions about the respondents' health compared to others (much better, better, the same, worse, or much worse) and about the presence of any chronic diseases.

Specially trained bilingual interviewers from the University of California, Irvine, Center for Survey Research conducted the survey. They chose as the respondent the adult member of a household who had the most knowledge about the health care of the family. This person responded to questions about access to health care for the entire family, for an adult designate (the household member older than 17 years with the most recent birthday), and for a child designate (the household member younger than 18 years with the most recent birthday). This approach allowed for a random selection of adult and child household members. The interviewers initiated calls at various times of day and evening and made a minimum of six attempts to reach each family. They gave the respondents the option of completing the questionnaire in either English or Spanish. The survey took about 22 minutes to complete.

We used descriptive statistics to provide an overview of the results and the two-tailed χ^2 test to analyze dichotomous variables. In addition, we used logistic regression to evaluate the relative contributions of ethnicity, income, health insurance, employment, and health status in predicting access to medical care. In constructing the logistic regression model, we included variables that previously have predicted medical care access and all variables that showed an association on initial χ^2 testing ($P<.01$). We calculated odds ratios and 95% confidence intervals for the various subgroups.[4]

The university's Human Subjects Review Committee reviewed and approved the study protocol.

Results

In the October 1987 survey, we contacted 973 families who met the income criteria, of whom 652 (67%) agreed to participate. In the February 1988 survey, we contacted 473 families who met the income criteria, and 306 (65%) agreed to participate. Thus, we interviewed a total of 958 families.

Demographic Characteristics

Among the 958 families, 197 were Latino, 680 were Anglo, and 81 were from other ethnic groups. Of the 197 Latino families, 54 were undocumented, 137 were US citizens or permanent legal residents (whom we considered citizens), and 6 did not provide information about immigration status. The analysis included only those Latinos who provided such information. The 81 respondents categorized as "other" composed diverse ethnic groups, with small numbers from any one group, and were not analyzed.

Table 1 shows the demographic characteristics of adult Latinos and Anglos. Compared with Anglos, Latino citizens were younger, poorer, and more likely to be employed. Likewise, compared with Latino citizens, undocumented Latinos were younger, more likely to be men, poorer, and more likely to be employed.

Statistical Analysis

Univariate. According to all measures of access to medical care analyzed in this study (Table 2), Latino citizens had less access than Anglos. Compared with Anglos, they more often lacked health insurance ($P<.01$), a regular source of care ($P<.01$), and a physician visit within the previous year ($P<.01$). They were also more likely than Anglos to perceive access to medical care as difficult ($P<.01$) and that medical care created financial difficulty ($P<.01$). Not surprisingly, language was also more likely to create barriers to access among Latino citizens than among Anglos ($P<.01$).

Although undocumented Latinos lacked health insurance more often than did citizens ($P<.01$), 40% of the undocumented Latinos had some form of health insurance, usually provided by their employers. Undocumented Latinos also reported difficulty obtaining care more often than did citizens ($P<.01$). No significant differences existed between these groups in other access measures, such as regular source of care, physician visit during the previous year, financial barriers, and language.

Multivariate. Logistic regression, with control for age, sex, employment status, health status, and income, revealed that although Anglo versus Latino ethnicity did not emerge as a strong predictor of access, insurance status was a very strong predictor (Table 3). Insured respondents were less likely than uninsured respondents to lack a regular source of care (odds ratio 0.3, confidence interval [CI] 0.2 to 0.4) and to report no physician visit within the previous year (odds ratio 0.4, CI 0.3 to 0.6). Other variables also predicted access to care to a lesser extent. For instance, after controlling for other variables, poor respondents tended to be more likely than nonpoor respondents to lack a regular source of care (odds ratio 1.5, CI 0.9 to 2.6) and to report no physician visit during the previous year (odds ratio 1.4, CI 0.8 to 2.7).

TABLE 2.—*Measures of Access to Medical Care Among Latino and Anglo Adults and Families*

Measure of Access	Latino: All (n = 191), %	Latino: Undocumented (n = 54), %	Latino: Citizen (n = 137), %	Anglo (n = 680), %
Adult Designates*				
Lack health insurance	44	60†	38‡	16
No regular source of care	29	37	26‡	17
No physician visit in the previous year	23	24	23‡	11
Families§				
Access was somewhat or very difficult	21	30†	17‡	8
Medical care created financial difficulty	35	41	33‡	22
Language created difficulty in obtaining care	24	33	20‡	2

*Respondents answered these questions about access for the adult designate.

†$P<.01$, which is the difference in frequency of an access measure between Latino citizens and undocumented Latinos by 2-tailed χ^2 testing.

‡$P<.01$, which is the difference in frequency of an access measure between Latino citizens and Anglos by 2-tailed χ^2 testing.

§Respondents answered these questions about access for the whole family. For example, "Is medical care very difficult, somewhat difficult, somewhat easy, or very easy to obtain for your family?"

Adults in the work force (employed and unemployed) were more likely than adults not in the work force to lack a regular source of care (odds ratio 2.0, CI 1.3 to 2.2) and to report no physician visit during the previous year (odds ratio 1.6, CI 1.0 to 2.7). Persons younger than 65 years also tended to have less access to health care. For instance, adults younger than 65 were more likely than older adults to report no physician visit in the previous year (odds ratio 1.6, CI 0.8 to 3.2).

Discussion

Latinos, whether citizens or undocumented, reported less access to medical care than Anglos by all measures used in this survey. The most important explanation for these findings was the relatively low prevalence of Latino families with health insurance. A lack of health insurance was reported by 38% of Latino citizens and 60% of undocumented Latinos. The percentage of uninsured Latino citizens exceeded the 31% found in a recent national access survey.[1] Overall, Latinos were nearly three times more likely than Anglos to be uninsured. Moreover, multivariate analysis confirmed insurance status as the strongest predictor of access to medical care.

We found surprisingly few differences in access between undocumented Latinos and Latino citizens. As expected, those in the undocumented group were less likely to possess health insurance. In California, this group is not entitled to government-sponsored insurance except for coverage of prenatal and emergency care. By other measures of access, however, such as regular source of care and visiting a physician in the previous year, no significant differences existed between the undocumented and Latino citizens. The results emphasize that access to medical care was limited for all Latinos in this study.

TABLE 3.—*Predictors of Lack of Access to Medical Care**

Predictor Variable	No Regular Source of Care: Odds Ratio (95% CI)†	No Physician Visit Within the Previous Year: Odds Ratio (95% CI)†
Anglo heritage	0.9 (0.6-1.6)	1.3 (0.8-2.3)
Age < 65 yrs.	1.2 (0.7-2.2)	1.6 (0.8-3.2)
Female sex	0.8 (0.6-1.3)	1.1 (0.7-1.7)
In the work force	2.0 (1.3-3.2)	1.6 (1.0-2.7)
Income status		
Poor	1.5 (0.9-2.6)	1.4 (0.8-2.7)
Nearly poor	1.0 (0.6-1.7)	1.5 (0.9-2.5)
Insured	0.3 (0.2-0.4)	0.4 (0.3-0.6)

CI = confidence interval

*The logistic regression models controlled for ethnicity, age, sex, employment status, income, insurance status, and health status.

†The odds ratios are given for Anglos compared with Latinos, respondents younger than 65 years compared with those older than 65 years, for women compared with men, for respondents in the work force compared with those not in the work force, for the poor compared with the nonpoor, for the nearly poor compared with the nonpoor, and for the insured compared with the uninsured.

Our findings do not support the notion that health beliefs in the traditional Mexican culture strongly influence the behavior of Latinos seeking medical care. After controlling for age, sex, employment status, insurance status, income, and health status, ethnicity was not a strong predictor of access. The findings do support results of recent studies that have stressed the importance of socioeconomic factors as the causes of underusing health services.[5-8] For example, Chavez found that a belief in folk illnesses and folk practitioners did not significantly deter Mexican immigrants from seeking conventional medical care in San Diego, California.[8] He concluded that the primary reasons for underusing health services were economic and, for the undocumented, the fear of being deported.

Limitations of the study are inherent in surveys of this type. The data are self-reported and therefore based on respondents' memories. The sample excluded households without telephones, but in similar surveys, the omission of such households has not significantly altered the findings.[9] Finally, undocumented persons may have been reluctant to reveal their immigration status to the interviewers. If so, we may have included some undocumented Latinos in the Latino citizen group.

Our results have important health policy implications for improving access to medical care among Latinos. Most important, they suggest that providing health insurance for Latinos would improve their access to care. National polls indicate widespread public support for health care reform in this country ("The Times Poll—Majority Favors Reform of US Health Care System," *Los Angeles Times*, February 4, 1990, p A-1), and many proposals for universal health insurance are being discussed (J. Kosterlitz, "Kennedy's New Tack," *National Journal* 1987; 19:608-611).[10,11] If health insurance were made available to all Americans through a national health program, access for Latino citizens would likely improve. Such a program, however, must also address other barriers faced by poor Latinos because the insured poor tend to report less access than the insured nonpoor.

Providing health insurance for US citizens will not address the problem of limited access for undocumented Lati-

nos who live and work in the United States. Despite recent changes in immigration laws, undocumented immigration is likely to continue as long as economic underdevelopment continues in Mexico and Central America and as long as jobs are available in the United States. Therefore, plans for providing health insurance to the undocumented population should be considered. Rumbaut and co-workers found that long-term undocumented immigrants would participate in a health insurance plan if the costs were manageable within their family incomes and if they could participate without being asked about immigration status.[12] These investigators suggested that partial funding for such a program should come from federal sources because the federal treasury receives most of the undocumented immigrants' taxes.

Finally, our results point out the importance of studying local conditions when planning health policies. For example, by some measures Latinos in Orange County experience less access to medical care than a national sample. Moreover, Latino citizens and undocumented Latinos face similar barriers to access. Such local findings are not evident in national investigations. The results of community-oriented research may be used to guide the development of new health care programs and to influence public funding for indigent health care services.[13]

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Articles

Travel Medicine for the Primary Care Physician

ALEX STUDEMEISTER, MD, *San Jose, California*

Travel medicine has become an important aspect of primary care. More than 8 million Americans travel to developing countries each year,[1] and of these a quarter have at least one illness develop during their sojourn.[2] Travelers are at risk of acquiring a number of preventable infections, such as travelers' diarrhea, viral hepatitis A, and malaria (Table 1).[2-7] Sources of information are available that describe in detail prophylactic measures and immunizations for travelers (Table 2). The following is an overview of vaccinations and prophylactic regimens that can be readily provided by primary care physicians.

General Recommendations

Before traveling to underdeveloped areas, each patient should be instructed on preventive measures against travelers' diarrhea. Consideration should also be given to the need for vaccinations and malaria chemoprophylaxis. Patients with any significant chronic illness should have a complete medical evaluation in advance and consider taking along a medical summary, a list of medications with written prescriptions, and any relevant studies, such as a copy of an electrocardiogram. A first-aid kit consisting of adhesive strips and gauzes, insect repellent, aspirin, antacid, antibiotic ointment, sun-guard lotion, lip balm, antimotion sickness medication, thermometer, extra glasses, and moleskin may be useful.

Table 3 lists the methods of administering commonly used vaccines. Yellow fever and cholera vaccines, with proper documentation in the International Certificates of Vaccination, are required to gain entry into certain countries. Meningococcal vaccination is required for entry into Saudi Arabia. More than three vaccinations should not be given simultaneously because of the possibility of increased side effects. On theoretic grounds, live vaccines—measles, mumps, rubella, yellow fever, oral poliovirus—should be avoided in immunocompromised persons and during pregnancy. Details regarding vaccination requirements and administration can be obtained from the publication, *Health Information for International Travel.*[8]

Travelers' Diarrhea

Acute diarrhea, which in most cases is a mild illness lasting less than a week, occurs in 20% to 50% of travelers to developing countries.[8] Enterotoxigenic *Escherichia coli* is the most frequently identified cause of travelers' diarrhea; other causes include *Salmonella, Shigella, Campylobacter,* and *Giardia* species, *Entamoeba histolytica,* and viruses. Elderly persons and patients with achlorhydria, gastric resection, or immune deficiency are at increased risk for travelers' diarrhea.

Travelers can protect themselves by drinking only bottled beverages or purified water. Boiling is the most reliable way to purify water. Bringing the water to boil should be adequate, except at high altitudes, where it should be boiled for several minutes. Alternatively, 5 drops of tincture of iodine can be added per quart (or liter) of clear water 30 minutes before drinking. Cold or turbid water requires 10 drops and a delay preferably of several hours before it is drunk. Portable water filters may offer some protection, but they have not been extensively tested and the Centers for Disease Control (CDC) make no specific recommendations regarding their use. Travelers should not consume ice, uncooked food, unpasteurized milk, and fruit that cannot be peeled.

The use of antibiotics, such as doxycycline (100 mg daily), double-strength trimethoprim-sulfamethoxazole (once a day), and norfloxacin (400 mg daily), and of bismuth subsalicylate (2 oz or two tablets four times a day) is effective in preventing travelers' diarrhea.[8,9] These preventive measures are not recommended for the average traveler, however, because of the benign nature of the illness and the risk of side effects from prophylactic antimicrobials. Prophylaxis should be considered for persons at high risk for acquiring travelers' diarrhea who may have substantial morbidity from this illness.

Travelers' diarrhea usually resolves without specific therapy. Bismuth subsalicylate and antimotility agents, such as loperamide hydrochloride and diphenoxylate hydrochloride, may provide temporary relief in mild cases (Table 4). Fluid therapy consisting of juices, caffeine-free soft drinks, and soup or an oral replacement solution as recommended by the United States Public Health Service (Table 5) should be part of the treatment of any diarrheal illness.

Travelers to underdeveloped areas may benefit from early, self-treatment of travelers' diarrhea, especially if diarrhea is associated with fever and blood or mucus in the stools. Treatment with three- to five-day regimens of the combination drug trimethoprim and sulfamethoxazole, trimethoprim alone, doxycycline, and ciprofloxacin (Table 4) may be effective.[8,10] Fluoroquinolones have the advantage of a broad spectrum of activity that includes *Campylobacter* species. The combination of sulfamethoxazole-trimethoprim and loperamide is also effective therapy.[11] If diarrhea persists for more than three days, further medical evaluation should be carried out promptly to rule out intestinal parasites and other causes of diarrhea.

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From the Department of Medicine, Section of Infectious Diseases, San Jose Medical Group, San Jose, California.
Reprint requests to Alex Studemeister, MD, Department of Medicine, Section of Infectious Diseases, San Jose Medical Group, 45 S 17th St, San Jose, CA 95112.

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
HAV = hepatitis A virus
HDCV = human diploid cell [rabies] vaccine
OPV = oral poliovirus vaccine

TABLE 1.—*Frequency of Infections in US Travelers*

Infection	*Cases/100,000 Travelers*	*Reference*
Travelers' diarrhea	30,200	Kendrick, 1972[2]
Viral hepatitis A	300	Kendrick, 1972[2]
Malaria	<20	Opez et al, 1979[3]
Typhoid fever	<17	Amler et al, 1982[4]
Measles	0.5	Ryan et al, 1989[5]
Meningococcal meningitis	0.05*	CDC, 1987[6]
Cholera	0.02	Snyder and Blake, 1982[7]

CDC = Centers for Disease Control

*Among pilgrims returning from Mecca and Medina, Saudi Arabia.

TABLE 2.—*Sources of Informotion for Trovel Medicine*

References

Centers for Disease Control (CDC): *Health Informotion for Internotionol Trovel.* Superintendent of Documents, Government Printing Office, Washington, DC 20402, telephone (202) 783-3238

CDC: Weekly Summary: Countries With Areas Infected With Quarantinable Diseases ("Blue Sheet"). CDC Center for Prevention Services, Division of Quarantine, Atlanta, GA 30333

American Society of Tropical Medicine and Hygiene: *Health Hints for the Tropics,* Karl A. Western MD (Ed): Tropical Medicine and Hygiene News, 6436 31st St, NW, Washington, DC 20015-2342

Goldsmith R, Heyneman D (Eds): *Tropicol Medicine and Porositology.* Norwalk, Conn, Appleton & Lange, 1989

Telephone Sources

Public Health Service Quarantine Station: Chicago (312) 686-2150, Honolulu (808) 541-2552, Los Angeles (213) 215-2365, Miami (305) 526-2910, New York (718) 917-1685, San Francisco (415) 876-2872, Seattle (206) 442-4519

CDC, travel recommendations: (404) 332-4559

Information Sources for Patients

Bezruchka S: *The Pocket Doctor.* Seattle, Wash, The Mountaineers, 1988. Gives practical medical advice for laypersons

United States Department of State, Bureau of Consular Affairs: "Your Trip Abroad," "Travel Tips for Senior Citizens," "Tips for Travelers to... (different countries)"

Vaccinations Against Enteric Pathogens

Avoiding potentially contaminated food and water is the best protective measure against cholera, typhoid fever, viral hepatitis A, and poliovirus infections. Vaccination against these infections is indicated for travelers likely to have exposure to contaminated food and water in underdeveloped areas and for persons, such as Peace Corps volunteers and health care workers, who plan to reside in endemic areas.

Cholera, which is characterized by vomiting, watery diarrhea, and dehydration, rarely occurs in American travelers. Most cases follow exposure to contaminated water supplies in cholera-endemic areas of sub-Saharan Africa, Asia, the Indian subcontinent, and Latin America. Persons likely to have considerable exposure to unsanitary conditions in endemic areas should receive cholera vaccination. Certain countries in Asia and Africa require cholera vaccination for entry if travelers have been in a region reporting an outbreak of cholera. A listing ("blue sheet") of countries reporting cholera outbreaks is provided by the CDC (Table 2).

The cholera vaccine is only 50% effective in reducing the incidence of cholera. A single dose given at least six days before departure, with proper validation of the International Certificate of Vaccination, satisfies entry requirements. Cholera and yellow fever vaccines should be given at least three weeks apart or concurrently if time does not permit this.

More than two thirds of cases of typhoid fever in the United States follow foreign travel.[5] Typhoid fever is a serious illness and widely prevalent in underdeveloped countries. Vaccination against *Salmonella typhi* should therefore be considered for all travelers who plan to visit or reside in regions with poor sanitary conditions. Typhoid fever may occur even after vaccination with the heat-killed *S typhi* vaccine, pointing to the importance of adhering to food and water precautions. A live oral typhoid vaccine containing the attenuated strain of *S typhi,* TY 21A, has recently become available. The live oral vaccine is preferred over the injectable vaccine because of fewer side effects with its use.

Viral hepatitis A varies in severity from a mild illness to fulminant, life-threatening hepatic failure and is therefore a significant health risk to travelers to underdeveloped areas. Immune globulin protects against this infection and should be given to both short- and long-term travelers likely to have

TABLE 3.—*Voccinotions Commonly Used for Internotionol Trovel**

Vaccine	*Dosing Schedule*	*Booster Interval*	*Precautions*
Cholera	2 doses 4 wk apart	6 mo	...
Immune globulin for HAV	2 ml for 3-mo stay 5 ml for 6-mo stay	... ...	Avoid concurrent live vaccine except yellow fever and oral poliovirus vaccine (OPV)
Measles	1 dose before trip if susceptible	...	Avoid if immunosuppressed or pregnant
Meningococcal	1 dose	3 yr	...
Poliovirus	1 dose (booster)	Not determined	Do not use OPV if immunosuppressed recipient or household member or pregnant; use eIPV if immunosuppressed
Rabies	3 doses on days 0, 7, and 21 or 28	2 yr	...
Tetanus and diphtheria	1 dose (booster)	10 yr	...
Typhoid	2 doses 4 wk apart† 4 doses 2 days apart‡	3 yr ...	... ...
Yellow fever	1 dose	10 yr	Avoid if immunosuppressed or pregnant

eIPV = enhanced-potency inactivated poliovirus vaccine, HAV = hepatitis A virus

*From the Centers for Disease Control.[8]
†Given subcutaneously.
‡Given orally.

exposure to contaminated food and water in Latin America, Asia, or Africa. Immunity to the hepatitis A virus (HAV), as demonstrated by a positive anti-HAV titer, obviates the need for repeated immune globulin injections for the frequent traveler to high-risk areas.

Immune globulin is usually given just before departure. Live virus vaccines, except for oral polio vaccine and yellow fever, should be given at least two weeks before, or at least six weeks (preferably three months), after immune globulin administration. Whether immune globulin protects against non-A, non-B hepatitis, which has recently caused outbreaks of enterically transmitted hepatitis in parts of Asia, Africa, the Middle East, and Central America, is not known.

Poliovirus Vaccination

Poliomyelitis remains endemic in many underdeveloped countries as a result of crowding and poor sanitary conditions. The virus is transmitted mainly by shedding from the throat and gastrointestinal tract of asymptomatic persons.

TABLE 4.—*Treatment of Travelers' Diarrhea**

Fluid and salt replacement	Soft drinks, juice, soup, oral replacement solution (Table 5)
Antimotility agents	
Loperamide HCl	2 capsules initially, then 1 with each loose stool
Diphenoxylate HCl	2.5 mg every 6 h
Bismuth subsalicylate	2 oz every ½ hr for 4 h
Antibiotics†	
Trimethoprim-sulfamethoxazole DS	Twice a day
Trimethoprim	200 mg twice a day
Doxycycline	100 mg twice a day
Ciprofloxacin	500 mg twice a day

DS = double strength, HCl = hydrochloride

*Choose 1 or more of these regimens, depending on severity of illness.
†Antibiotics should be taken for 3 to 5 days.

TABLE 5.—*US Public Health Service Oral Replacement Salutian**

Prepare 2 glasses as follows, drink from each alternately until thirst resolved, and supplement with boiled water, carbonated beverage, or tea

Glass 1
Fruit juice . . . 8 oz.
Honey or corn syrup . . . ½ tsp
Table salt . . . 1 pinch

Glass 2
Water . . . 8 oz
Baking soda . . . ¼ tsp

*From Centers for Disease Control.[8]

About 20% of young adults in the United States are susceptible to poliovirus infection.[12] Of the 118 cases of poliomyelitis occurring in the United States between 1975 and 1984, 12 (10%) were imported cases among US citizens.[13] Previously vaccinated travelers planning to visit or reside in areas with poor standards of hygiene and sanitation should receive a booster dose of polio vaccine. Unvaccinated persons should complete the primary series.

The oral poliovirus vaccine (OPV) is a live virus vaccine consisting of three virus serotypes. A booster dose of OPV is generally given to previously immunized persons before travel to high-risk areas. Because of the risk of vaccine-associated paralysis, immunosuppressed persons or those living with someone who is immunosuppressed should not receive OPV. Unimmunized or immunosuppressed persons should receive enhanced-potency inactivated poliovirus vaccine (eIPV), which consists of formalin-inactivated virus. If time does not permit administering the complete primary doses of polio vaccine to an unimmunized traveler, two doses of the vaccine four weeks apart, or a single dose before departure, should be given.

Measles, Mumps, and Rubella Vaccinations

Measles, mumps, and rubella, endemic throughout the world, are transmitted mainly through direct contact with infected children or their aerosolized respiratory secretions. Many Americans remain susceptible to measles as a result of improper vaccination or vaccine failure.[14] Most adults in the United States are immune to mumps and rubella, although outbreaks within closed communities continue to occur. Susceptible travelers to underdeveloped areas should be vaccinated against these infections.

Measles revaccination is recommended for susceptible travelers born after 1956 who will be visiting high-risk areas. Persons are considered immune to measles if they were born before 1957, received proper measles vaccination, or have documentation of physician-confirmed measles or laboratory evidence of immunity. Mumps and rubella vaccinations should be given to persons lacking previous vaccination, documentation of physician-diagnosed illness, or laboratory evidence of immunity. Persons susceptible to at least two of these infections may be immunized with the measles-mumps-rubella vaccine without an increased risk of vaccination-associated side effects.[8]

Meningococcal Vaccination

As a result of overcrowding, meningococcal meningitis occurs sporadically and in small outbreaks in many underdeveloped regions of the world. Major epidemics involving large areas are common in sub-Saharan African countries

TABLE 6.—*Drugs Used for Malaria Chemaprophylaxis**

Drug	*Adult Dose*	*Indications*
Chloroquine phosphate	300-mg base or 500-mg salt weekly	Travel to areas of chloroquine susceptibility
Mefloquine	250 mg weekly	Travel to areas of chloroquine or Fansidar resistance
Pyrimethamine and sulfadoxine (Fansidar)	3 tablets all at once	Presumptive therapy in areas of chloroquine resistance when taking chloroquine
Doxycycline	100 mg daily	Travel to areas of chloroquine or Fansidar resistance
Primaquine	15-mg base or 26.3-mg salt daily for 2 wk	Long-term stay in endemic area to prevent vivax or ovale malaria

*From Centers for Disease Control.[8]

("meningitis belt"). Persons traveling to countries within the meningitis belt and to regions reporting outbreaks of meningococcal meningitis, such as Nepal and New Delhi (India), should receive the meningococcal vaccine before departure. Pilgrims and visitors to Mecca (Saudi Arabia) are required to be vaccinated against meningococcal meningitis not more than two years and at least ten days before arriving in Saudi Arabia.

The meningococcal vaccine (Menomune) is a quadrivalent A/C/Y/W-135 vaccine composed of capsular polysaccharides. The duration of efficacy is not well established but appears to be at least three years. It is available in single-dose and multidose vials with limited storage life after it has been opened.

Rabies Vaccination

Rabies is endemic in Latin America, Africa, and most of Asia. Dogs are the major source of human rabies in underdeveloped countries. Persons planning to stay for more than 30 days in rabies-endemic countries should receive pre-exposure prophylaxis. Between 1975 and 1984, six United States citizens acquired rabies while living in a foreign country.[15] A failure to receive adequate postexposure therapy played a major role in these cases. It is therefore important to inform travelers to endemic areas of the risk of rabies and the need for postexposure management following high-risk exposure.

Pre-exposure prophylaxis consists of three doses of human diploid cell rabies vaccine (HDCV), which is an inactivated virus vaccine prepared from fixed rabies virus grown in human diploid cell culture. Immunization should be completed at least 30 days before departure. The use of chloroquine phosphate may interfere with the response to HDCV, particularly when it is given by the intradermal route.[8] Therefore, HDCV should be given intramuscularly whenever a traveler is taking chloroquine. Persons residing in endemic areas should have booster immunization or serologic testing of antibody level every two years.

Postexposure rabies treatment in persons having received pre-exposure prophylaxis consists of immediate wound care with soap and water and two doses of HDCV. Nonimmunized persons require the administration of both HDCV and human rabies immune globulin. Details regarding pre-exposure immunization and postexposure treatment are available from the references listed in Table 2.

Yellow Fever Vaccine

Yellow fever is transmitted by mosquitoes and is characterized by high fever, hepatitis, and hemorrhagic shock. It affects mainly unvaccinated persons residing in endemic areas of South America and Africa. Yellow fever has occurred in unvaccinated travelers visiting rural areas of Africa.[16] Travelers to rural areas of equatorial South America and Africa should be vaccinated. Immunization against yellow fever with a properly validated International Certificate of Vaccination is required for entry into several countries of South America and Africa.

Yellow fever vaccine is a live, attenuated virus (17 D strain) available only at registered yellow fever vaccine centers. The presence of an anaphylactic egg allergy or an immunosuppressed state is a contraindication. Pregnant women should be advised not to travel to a yellow fever-endemic area. If travel to a high-risk area is unavoidable, however, the yellow fever vaccine should be given.[16]

Miscellaneous Vaccinations

All travelers should be up-to-date with respect to tetanus prophylaxis before departure. Persons at risk of exposure to blood or blood products, such as health care workers, or those who might have sexual contact in areas endemic for hepatitis B virus infection, should be vaccinated against this infection. Because influenza can occur throughout the year in the tropics, persons in the high-risk categories should be immunized with the current influenza vaccine. Other vaccinations, such as those against plague and Japanese encephalitis, are indicated depending on the itinerary and risk of exposure as detailed in *Health Information for International Travel.*[8]

Malaria Prophylaxis

Malaria is a substantial health risk to persons traveling to rural regions of Central and South America, sub-Saharan Africa, Asia, the Indian subcontinent, the Middle East, and Oceania. From 1978 until 1982, about 1,300 imported cases of malaria among US citizens were reported.[17] Most fatal cases are caused by *Plasmodium falciparum* and are related to inadequate chemoprophylaxis and delayed diagnosis and treatment.[18] None of the chemoprophylactic regimens are completely protective against malaria. Therefore, travelers should be advised to seek medical care if symptoms of malaria develop during their stay in or after they leave a malarious area, even if they have taken the prescribed chemoprophylactic drugs.

Drugs currently used for malaria chemoprophylaxis are listed in Table 6. Chemoprophylaxis is started one or two weeks before departure and continued for four weeks after leaving the malarious area. The standard regimen of the weekly administration of chloroquine is not adequate in many parts of the world as a result of the spread of chloroquine-resistant strains of *P falciparum.* The CDC recommends the use of mefloquine for malarial chemoprophylaxis during travel to areas with chloroquine-resistant *P falciparum.*[19] A less desirable regimen consists of the weekly use of chloroquine with the use of a treatment dose of pyrimethamine-sulfadoxine (Fansidar) for presumptive but incomplete therapy for falciparum malaria.

Strains resistant to both chloroquine and pyrimethamine-sulfadoxine have emerged in certain areas of the world such as Thailand, Burma, and Kampuchea. The use of mefloquine is recommended for travelers to these areas. An alternative regimen consists of the daily administration of doxycycline; the possible side effects of prolonged doxycycline use, however, are not well established. Travelers taking doxycycline should be warned of photosensitivity, candidal vaginitis, and other side effects.

Primaquine phosphate, which eliminates hepatic infection by *Plasmodium vivax* and *Plasmodium ovale,* should be given to persons, such as Peace Corps volunteers and missionaries, who have had prolonged exposure in malaria-endemic areas. It is usually administered during the last two weeks of the four-week course of prophylaxis after leaving a malarious area. Even in persons with short-term exposure, vivax malaria can develop that will not be cured with chloroquine therapy alone. Travelers should be advised that symptoms can arise from vivax infection several years after exposure if primaquine is not used.

Important personal protective measures against malaria

and other illnesses transmitted by mosquitoes, such as yellow fever and dengue, include sleeping in well-screened rooms, using mosquito nets, covering arms and legs when outdoors, and using a mosquito repellent containing *N,N*-diethyltoluamide (deet). Because high doses of deet may cause neurotoxicity, optimally a 32% lotion is recommended. Travelers to high-risk areas should consider taking along a pyrethrum-containing insect spray for use in living and sleeping areas if they are not allergic to these products.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the Special Editors.

STEPHEN M. McPHEE, MD
TERRIE MENDELSON, MD
Special Editors

Mentors and Role Models for Women in Academic Medicine

WENDY LEVINSON, MD; KAREN KAUFMAN, MA; BRINTON CLARK; *and* SUSAN W. TOLLE, MD, *Portland, Oregon*

Senior mentors and role models have a positive influence on the career advancement of junior professionals in law, business, and medicine. In medicine an increasing number of women are pursuing academic careers, but available senior mentors to provide career guidance are often lacking. We report on the results of a national survey of 558 full-time faculty women, aged 50 years and younger, in departments of medicine in the United States, regarding their experience with role models and mentors. Women with mentors report more publications and more time spent on research activity than those without mentors. Women with a role model reported higher overall career satisfaction. This report, with illustrative examples, may be helpful to other women pursuing academic careers and to physicians who serve as mentors or role models to others.

(Levinson W, Kaufman K, Clark B, Tolle SW: Mentors and role models for women in academic medicine. West J Med 1991 Apr; 154:423-426)

The value of senior mentors to career advancement has been demonstrated in several professions including law, business, and medicine.[1-3] Both men and women professionals benefit from having senior mentors, but for women, senior mentors to provide them with career guidance are more frequently unavailable. Research about academic professionals shows that junior faculty with mentors publish more articles,[4] feel more confident in their capabilities,[5,6] and are more satisfied overall with their career than those without mentors.[7]

With the changing demographics of medicine, there are increasingly more women entering junior faculty positions in medical schools.[8] At present, junior faculty women are more likely to leave the path leading to academic advancement than their male colleagues.[9] What role do mentors currently play in encouraging and sustaining women's academic careers? A recent survey of full-time faculty women in departments of medicine in the United States indicated that 40% did not have a mentor during their training and 67% had no current relationship with a successful role model.[7] In this article we examine further the importance of mentors and role models to women in academic medicine. While previous studies have explored some relationships between mentoring and career advancement, we examine the availability of mentors and role models to women in academic medicine and describe the diverse experiences of women currently in academic medicine. Illustrative examples ranging from helpful to suboptimal mentor relationships are included. We hope that describing the experiences of these women will be useful to other women physicians currently pursuing academic careers and to physicians who serve as mentors or role models to junior faculty and medical students. In addition, we hope this report will provide guidance to women medical students thinking of developing a career in academic medicine by informing them about the value and characteristics of a good mentor.

Methods

In January 1988, a 110-item survey was mailed to all women 50 years of age and younger in departments of medicine (n = 862) listed in the September 1987 faculty roster of the American Association of Medical Colleges (AAMC). The faculty roster is based on information provided to the AAMC by the office of the dean of each medical school and is updated monthly. The roster includes all full-time faculty who are willing to be listed. Our survey instrument requested demographic information, specific details about child rearing and childbearing, and attitudes toward both personal and professional issues. We specifically requested information about mentors and role models. More than 83% of those surveyed returned their questionnaires (n = 558). The mean age of the respondents was 38 years. Most (64%) were assistant professors, but 25% held more senior academic ranks (5% professor and 20% associate). The responses of selected survey items related to childbearing and child rearing were recently reported.[7] This article expands on the previous report by describing details from the questionnaire pertaining to mentors and role models.

All respondents were asked whether they had a mentor during their medical training and the sex of that mentor. Respondents were also asked whether they currently had a relationship with a role model who they perceived as successful in balancing career and personal life. We defined a mentor as an advisor whose guidance focuses on professional issues. In contrast, a role model may provide an example in a broader context that includes both professional and personal aspects of life. A role model may be emulated by a student. Respondents were encouraged to describe their personal experiences with mentors and role models.

Coders classified written comments and found that they clustered into seven major themes. Table 1 displays the seven categories and provides several representative examples of each. The first 100 questionnaires were scored by two separate coders to ensure accuracy in the coding; high interrater reliability was found ($r = .85$). The other 458 questionnaires were then coded by one person only.

Associations were analyzed by comparing tabulated data from the mentoring section with demographic information (rank and race) and with career demographics (time spent on research, number of publications, and overall career satisfac-

From the Internal Medicine Training Program (Dr Levinson), Clinical Research (Ms Kaufman and Mr Clark), Good Samaritan Hospital and Medical Center, and the Division of General Internal Medicine (Drs Levinson and Tolle), and Center for Ethics in Health Care (Dr Tolle), Oregon Health Sciences University School of Medicine, Portland.

Reprint requests to Wendy Levinson, MD, Good Samaritan Hospital and Medical Center, 2282 NW Northrup, Suite 24, Portland, OR 97210.

tion). Career satisfaction scores were based on responses to three questions with a Likert scale format. We used *t* tests to examine the association between having a mentor during training or a current role model and personal or career demographics.

As previously reported, overall, 61% of respondents acknowledged having had helpful relationships with a mentor of either sex during their training, and 39% recounted no such relationship.[7] In addition, 31% of respondents said they had an ongoing relationship with role models perceived as successful in balancing career and personal life, whereas 67% had no such relationship.[7]

Results

Of the 558 women who returned surveys, 236 (42%) volunteered at least one comment about mentors or role models. Those responses were grouped into seven major themes (Table 1). Major themes included difficulty finding a mentor, either male or female; the lack of available senior women to serve as role models; having a relationship with a role model who provided professional but not personal guidance; peers serving as role models to one another; the respondent herself acting as a mentor or role model to others; experience with a good mentor or role model; experience with a poor mentor or role model.

Approximately 50 women commented on the lack of available senior women faculty to serve as role models. For example, one woman said, "I'm the only woman in the Department of Medicine." Another reported, "I have *never* had contact with a female tenured academic physician." In addition, 45 focused on the discrepancy between a role model in the professional versus the personal domains. Mentors might provide guidance or examples of successful teachers or researchers but not discuss the personal aspects of combining career and family. One respondent wrote, "There was never anyone who looked at me and my career plans in the context of my life outside of medicine—just mentors for life within medicine." In particular, respondents with children remarked that their academic mentors often did not have children or family responsibilities and did not serve as role models in combining career and family. One respondent said, "The few other women faculty with whom I work are unmarried or have elected not to have children in order to pursue a career. Most of my other female physician friends that married and had children are working in settings with fixed hours outside of academic medicine."

Those respondents who had good mentors and role models highly valued those relationships. Those "good" mentors helped respondents with research efforts, in obtaining salary benefits and protected research time, and provided encouragement and emotional support. Often these mentors were men, consistent with the greater availability of senior faculty men than senior women.

A significant association was found between having a mentor of either sex during training and the respondent's race, number of publications, time spent on research, and

TABLE 1.—*Responses to Survey of Women in Acodemic Medicine Regarding Mentors and Role Models*

Category	*Responses, No.*	*Example*
Difficulty in finding a mentor of either sex	22	This has been a major problem for me. Even in departments that welcome women, few males are willing to become their research mentors—and there aren't any women
		No such person was available during my training. Most mentors appear to be very busy and usually not helpful in dealing with issues in this study
		I feel this is a major lack, not so much a role model to balance personal life, but the lack of a mentor in both training and as junior faculty
Lack of available senior women to be mentors or role models	48	I have come across no female role models at the professor level in academic medicine in the institutions where I have worked
		No female mentors were accessible
Relationship with role model or mentor who provides professional but not personal guidance	44	Most women physicians I admire as professionals I could not model myself upon as people—they are not married, no kids, no other pressing outside interests, but they had integrity, hardworkingness (beyond the men), and a commitment to their patients as people upon which I modeled my professional life
		Yes, but more or less restricted to development of intellectual skills (excellent role models for developing reading habits, improving patient care skills, etc)—very little opportunities to discuss other issues (how to combine careers and personal life, etc)
Getting support from peers rather than role models	28	Mostly peers—male more than female with whom I discuss these issues—perhaps we complain, lament more than actually discuss, but it's helpful
Respondent now serving as a role model or mentor	14	At the time I trained there were very few women in medicine. I became a role model for others
		I've become one, which is sobering!
Experience with a good mentor or model	36	My mentor during nephrology fellowship was male and completely understanding [vis-à-vis] stresses of both job and home. His household was a two career household with children and he definitely carried equal responsibility
		She was definitely committed to family and career and gave me a great deal of emotional support as a resident
		A female academic general internist, 5 to 6 years my senior, single and without a family. Doggedly determined to succeed in academics and usually prepared to understand the complexities of my life. Encouraged me to enter academics anyway
Experience with a poor mentor or role model	9	One female attending assigned as my preceptor was more harmful than helpful—she was not supportive—she was too "superwoman"
		I had a destructive relationship with a male mentor who was intimidated by me and was only two years older than me (not the best for a mentor)

overall career satisfaction. White respondents were significantly more likely than nonwhite respondents to report having a mentor during training (63% versus 49%, $P<.05$). Those who had a mentor during training averaged 13.1 publications compared with 10.3 articles for respondents without a mentor ($P<.05$). Respondents who had a mentor also spent more time on research activities. Women with a mentor estimated they spend an average of 26% of their time on research activities, and those without a mentor spend 21% of their time doing research ($P<.01$). The sex of the mentor was not a significant influence on either the number of publications or the percent of time spent on research. As reported previously, those who had a mentor during their training also reported greater career satisfaction than those who had not had a mentor.[7] Present rank was not correlated with having a mentor during training.

A minority of women (31%) reported having a current successful role model. Women in lower ranks were more likely to have a role model than women of associate and professor rank ($P=.05$). Unlike with mentorship, the race of the respondent was not correlated with having a role model. Having a relationship with a role model has different career implications than does a relationship with a mentor. Overall career satisfaction was strongly associated with having a current role model ($P<.0001$), but a current relationship with a role model was not associated with either the percentage of time spent on research or the number of publications. Role models appear to provide more guidance about personal issues, such as combining career and family, than do mentors.

In addition, 36 respondents commented on the value of peers as role models. "Peers in similar situations to commiserate and compare notes with" serve as an important source of support and academic encouragement, particularly when senior mentors are not available.

Discussion

The value of a good senior mentor to the career advancement of a junior faculty member is unequivocal. The present study shows that women with mentors have more publications in peer-review journals, spend more time on research, and have greater career satisfaction than women without mentors. This is consistent with other studies of professional women both in medicine and other academic areas.[4-7] Because women physicians tend to have slower academic promotion rates and leave the academic path more frequently than men,[9] they likely have a greater need for mentors to encourage and sustain their careers. One physician summed up the importance of this need: "I believe that the absence of the successful mentor relationship in my career was a major impediment to its progress."

Finding a good senior mentor, however, particularly a female mentor, is not an easy task. What if a female mentor is not available? Does the sex of a mentor influence the efficacy of the relationship? Some sociologic studies suggested that mentors of the same gender as the student are more effective than one of the opposite sex.[10,11] This present study did not demonstrate a difference in research activities or number of publications dependent on the sex of the mentor during training. It is likely that mentors of either sex are equally effective in counseling women about career advancement. One respondent noted that "My immediate boss, and mentor [a man], has helped me to get salary increases, protected my research time, and supports lab efforts." On the other hand, personal guidance and support may be more effectively provided by same-sex mentors or role models. In this study, comments suggested that women role models could be most helpful in providing guidance about balancing personal and professional lives. One respondent said, "The chief of my division (a man) was extremely helpful and sensitive, but clearly the scope of his advice was limited." That male and female mentors for junior women faculty have different roles has been pointed out in a study by Ochberg and co-workers.[12] It shows that high-ranking male mentors who are effective career sponsors were less likely than female mentors to provide personal advice. Given this information, we would suggest that young women faculty not try to find "everything" in one senior mentor. Perhaps the most effective strategy is for junior faculty to seek a mentor of either sex to provide guidance in career issues and then to find a role model of their sex to provide advice and encouragement in issues related to combining career and family and personal development.

This study suggests another strategy for compensating for the lack of senior women role models. Using a network of peers can be a viable method to obtain social and career enhancement. Peers, in fact, offer the advantage of providing support at successive career stages, and sociologic studies have shown their effectiveness in both career and personal domains.[13] In response to the issue of the availability of role models successful at balancing career and personal life, one woman commented, "I don't consider them role models; I have colleagues/friends who do it in a variety of ways. We support each other."

Furthermore, this study shows an important relationship of race and mentoring. White faculty are more likely than nonwhite faculty to have a mentor during training. While the number of nonwhite faculty was small (n = 57), we think this is an accurate reflection of the experience of nonwhite academic physicians. This result is consistent with studies of African-American students in graduate and professional education.[14,15] Minority students and junior faculty are at greater risk for leaving the academic pathway than their white peers.[16] Perhaps this is in part because they do not have the support and encouragement of senior mentors who can guide their career development.

This study has several limitations and raises further questions. First, the study included only full-time women faculty. Those women who work part-time or who have left academia may have different experiences related to mentors and role models. In fact, we speculate that some women who have left full-time academic positions may have done so because of a lack of guidance by senior mentors. Second, the experience of women currently entering academic medicine may be different from that of the group surveyed. For example, some universities provide support groups for women faculty or hold special retreats to address the needs of women faculty.[17] In addition, the study does not include a matched cohort of men physicians to allow comparisons between the sexes.

With the increasing number of women entering medical schools, pursuing residency training, and joining academic faculties, there is an increased need for senior mentors of both sexes to encourage these young faculty in their academic careers. It is in the best interest of academic institutions to foster the careers of these women so they may realize their full scientific potential. As one respondent clearly articulated, "Having a relationship with a mentor is one of the most difficult areas for women seeking academic careers, espe-

cially given it is so critical to their success." Both institutions and individual faculty members can play a role in correcting the present problem of a lack of available mentors. Institutions should implement formal mentorship programs and reward senior faculty for their mentor role. The American College of Physicians in a recent position paper on promotion and tenure for women and minorities encourages medical schools to establish formal career counseling programs for junior faculty. The college suggests that such programs should designate skilled senior counselors for junior faculty members.[18] In addition, individual senior faculty members should recognize the vital importance of their advice to junior faculty and place a high priority on dedicating time to these relationships.

While it is the responsibility of the institution to develop counseling systems, we encourage junior faculty women to actively seek mentors of either gender who can provide them with guidance in career development and nurture their research and teaching potential. Even in a nurturing environment, junior faculty need to assume the initiative in securing senior mentors. Junior faculty should give careful thought to identifying mentors to match their needs and academic interests. Senior faculty members of either sex can provide key research and academic guidance. While effective in many areas, some mentors may not be attuned to the challenges of combining career and family. Hence, junior women may need to develop other relationships, often with peers, to meet these needs.

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Conferences and Reviews

Congestive Heart Failure
New Frontiers

Moderator
WILLIAM W. PARMLEY, MD

Discussants
KANU CHATTERJEE, MB, FRCP; GARY S. FRANCIS, MD; BRIAN G. FIRTH, MD, DPhil; *and* ROBERT A. KLONER, MD, PhD

This is an edited summary of an Interdepartmental Dean's Conference arranged by the Department of Medicine, University of California, Davis, School of Medicine, and the Department of Veterans Affairs, Martinez Medical Center, Martinez, California. Michael C. Geokas, MD, PhD, organized this conference.

Congestive heart failure is a common syndrome with high mortality in its advanced stages. Current therapy includes the use of vasodilator drugs, which have been shown to prolong life. Despite current therapy, mortality remains high in patients with severe heart failure. Potent new inotropic vasodilators have improved ventricular performance but have not prolonged life in patients with end-stage heart failure. Serious arrhythmias are implicated in the sudden deaths of 30% to 40% of patients with severe heart failure, but the benefits of antiarrhythmic therapy have not been established. Upcoming trials will address this question. Ventricular remodeling and progressive dilatation after myocardial infarction commonly lead to congestive heart failure; early unloading of the ventricle with an angiotensin-converting enzyme inhibitor may attenuate these events. These findings support the concept that angiotensin-converting enzyme inhibitors may be useful in managing heart failure of all degrees of severity, including left ventricular dysfunction and end-stage heart failure. Part of the damage that may occur with acute myocardial infarction, particularly in this era of thrombolysis therapy, is reperfusion injury, which may be mediated by oxygen-derived free radicals. Better knowledge of the mechanisms and treatment of myocardial infarction, the leading cause of congestive heart failure, may help prevent or attenuate the development of this syndrome.

(Parmley WW, Chatterjee K, Francis GS, Firth BG, Kloner RA: Congestive heart failure—New frontiers. West J Med 1991 Apr; 154:427-441)

WILLIAM W. PARMLEY, MD*: Each year, congestive heart failure, a syndrome affecting about 3 million persons or about 1% of the population, develops in about 400,000 Americans.[1] By age 75, the prevalence of this syndrome rises to about 10%. Congestive heart failure is now the most common hospital discharge diagnosis among patients older than 65 years. Over the past several years, the incidence and prevalence of this syndrome appear to have increased while mortality from cardiovascular diseases has progressively declined. This presumably reflects the fact that more people are living to ages when congestive heart failure becomes more prevalent.

In the Framingham study, five-year mortality after congestive heart failure developed was about 60% in men and 45% in women.[2] Currently about 50% of patients with class IV heart failure (symptoms at rest) die within a year. Death is sudden in about 40% of patients, indicating that severe arrhythmias also play an important role.[3]

Current therapy for congestive heart failure includes several steps, as outlined in Table 1. First, the cause of the heart failure should be determined to set the stage for appropriate therapy. Second, the relative importance of diastolic dysfunction must be evaluated. If this dysfunction is the primary pathophysiology, therapy must be chosen accordingly. Third, appropriate surgical correction should also be considered. This may include valve replacement to treat pressure or volume overload or revascularization procedures to treat severe widespread ischemia contributing to the heart failure. Fourth, nonpharmacologic approaches, such as reducing salt intake and physical and emotional stress, should be considered. Nonpharmacologic approaches usually do not produce major changes in the degree of heart failure but may offer some benefit.

Fifth, pharmacologic therapy should be considered. Recent data suggest that the use of diuretics, digoxin, or vasodilators can be considered as first-line therapy and that combining these three classes produces maximal hemodynamic effects.[4-6] Depending on the first agent chosen, either or both of the other two classes of drugs may be added as necessary. Because vasodilators have prolonged life in patients with moderate[4] to severe[5] heart failure, their use should be considered for all forms of congestive heart failure. If these agents produce insufficient hemodynamic benefits, the potent new inotropic agents should be considered.[7] For patients with dilated cardiomyopathy, some data suggest that administering β-blockers like low-dose metoprolol may produce some

*Professor of Medicine and Chief, Division of Cardiology, University of California, San Francisco, Medical Center.

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Reprint requests to Michael C. Geokas, MD, PhD, University of California Service, Department of Veterans Affairs, Martinez Medical Center (612/111), 150 Muir Rd, Martinez, CA 94553.

ABBREVIATIONS USED IN TEXT

cAMP = cyclic adenosine monophosphate
ISIS-2 = Second International Study of Infarct Survival

benefit.[8] The patient group likely to benefit most from this approach has not yet been identified but may include those with excess tachycardia. Antiarrhythmic therapy is of uncertain benefit.[9] In view of this uncertainty, it is at least reasonable to attempt to reduce such proarrhythmic factors as electrolyte imbalance and ischemia and to avoid the use of potent inotropic agents when possible.

Finally, if all these measures are inadequate, heart transplant should be considered for appropriate patients. Transplant patients have a dramatic reduction in mortality compared with the pool of patients with end-stage heart failure from which they are selected.[10] More important, transplants improve the quality of life considerably. A limited availability of donor hearts restricts transplant candidates to patients meeting general criteria, including terminal heart disease; no diabetes mellitus or other systemic disease; age younger than 55 to 65; good renal, pulmonary, and hepatic function; no active infection or ulcer disease; no pulmonary hypertension or severe peripheral vascular disease; and psychosocial stability.[10]

Despite these demonstrated benefits of conventional therapy for congestive heart failure, many new frontiers remain to be explored. This conference explores four important current questions regarding the management of congestive heart failure. In the first section, Kanu Chatterjee, MD, considers the value of the potent new positive inotropic agents and their potential for doing harm. In the second section, Gary Francis, MD, explores the problem of sudden death in patients with severe congestive heart failure. Do antiarrhythmic agents or other interventions have any place in the care of these patients? In the third section, Brian Firth, MD, discusses the importance of attenuating the development of congestive heart failure following myocardial infarction. Can vasodilator therapy with angiotensin-converting enzyme inhibitors prevent the dilatation and remodeling that occur after myocardial infarction and that then lead to end-stage heart failure? In the fourth section, Robert Kloner, MD, in collaboration with Karin Przyklenk, MD, discusses an important issue in the thrombolytic era—whether reperfusion damage to the heart can be limited following successful thrombolytic therapy in acute myocardial infarction. A better understanding of these four issues will clearly influence our future approach to patients with congestive heart failure.

TABLE 1.—*Steps in the Management of Congestive Heart Failure*

Determine cause
Evaluate importance of diastolic dysfunction
Correct surgically, where possible
Nonpharmacologic therapy
Restrict salt intake
Reduce physical and emotional stress
Pharmacologic therapy
Begin with vasodilator, diuretic, or digoxin
Add other 2 as necessary
Special considerations
β-Blocker for dilated cardiomyopathy
Antiarrhythmic therapy
Heart transplant, if appropriate and feasible

Promise and Problems of New Inotropic Agents

KANU CHATTERJEE, MB, FRCP*: The pharmacotherapeutic management of congestive heart failure has progressed considerably in the past two decades. Whereas diuretics and digitalis were the only drugs available for many years, vasodilators, including angiotensin-converting enzyme inhibitors, have now been added to the armamentarium. Vasodilators, especially angiotensin-converting enzyme inhibitors, have been shown to improve the prognosis of patients with moderate[4] to severe[5] congestive heart failure and should always be considered for the management of these patients.

Mortality, however, remains high in the sizable proportion of patients who fail to respond or become refractory to vasodilator therapy. In addition, unacceptable complications develop in some patients or they cannot tolerate vasodilators or angiotensin-converting enzyme inhibitors. Thus, the search continues for new therapeutic strategies and pharmacologic agents, including inotropic drugs. In this section I describe newer nonglycosidic inotropic drugs in clinical use or undergoing clinical trials in patients with heart failure.

Classification and Mechanisms of Action of Nonglycosidic Inotropic Drugs

The primary mechanism for increased contractility is increased intracellular calcium concentration or increased responsiveness of myofilaments to calcium. The two broad categories of nonglycosidic inotropic drugs, adrenergic and nonadrenergic agents, modulate calcium concentration and sensitivity by different mechanisms. Adrenergic agents include dopamine, dobutamine, dopexamine, propylbutyldopamine, bromocriptine, fenoldopam, ibopamine, levodopa, butopamine, denopamine, colforsin (forskolin), pirbuterol, albuterol (salbutamol), and xamoterol. Nonadrenergic agents include amrinone, enoximone, imazodan (CI-914), milrinone, pimobendan, piroximone, sulmazole, vesnarinone (OPC-8212), VD-CA 115, and VD-CA 212.

Mechanisms of Action of Adrenergic Agents

The pharmacophysiologic effects of the adrenergic agents result from an activation of the various subtypes of adrenoreceptors.

β-Adrenoreceptors. The activation of myocardial β_1-adrenoreceptors, which stimulates the adenylate cyclase-cyclic adenosine monophosphate (cAMP) system and promotes calcium influx, is associated with increased contractility.[11] Cardiac cAMP production can be increased by activating the catalytic unit of the adenylate cyclase system without stimulating β_1-receptors. This appears to be the primary mechanism of action of some adrenergic inotropic drugs such as colforsin.[12] The activation of non-β-receptors, such as glucagon receptors, is also associated with increased cAMP production.

Studies indicate that the activation of the β_2-receptors found in human myocardium results in cAMP production and increased contractility,[13] but β_2-receptor agonists also stimulate β_2-receptors in peripheral vascular beds and induce peripheral vasodilatation. Activation of the β_2-receptors found on prejunctional nerve terminals facilitates the release of neurotransmitters[14] and may also contribute to peripheral

*Professor of Medicine, Director of the Coronary Care Unit, and Associate Chief, Division of Cardiology, University of California, San Francisco, Medical Center.

vasodilatation. Thus, β_2-receptor agonists have the potential to enhance contractility and decrease left ventricular afterload.

α-Adrenoreceptors. The activation of myocardial α_1-adrenergic receptors is also associated with enhanced contractility,[15] but such stimulation does not increase adenylate cyclase activity. It has been proposed that alterations in the polyphosphoinositide second-messenger system may mediate the action of myocardial α-receptors. At present, the existence and relevance of α_1-receptors in human myocardium remain uncertain. Furthermore, currently available adrenergic agonists also activate peripheral α-receptors. The activation of α_1-receptors in postganglionic effector cells is associated with a contraction of vascular and nonvascular smooth muscles.[16] The stimulation of α_2-receptors inhibits neuronal release of the neurotransmitters, and the activation of postjunctional α_2-receptors induces vasoconstriction.[17] Thus, the clinical use of α-agonists is limited to the treatment of hypotension.

Dopamine receptors. Two subtypes of dopamine receptors have been recognized.[18] The activation of dopamine$_1$ receptors is associated with the dilatation of renal, mesenteric, coronary, and cerebral vascular beds. The stimulation of dopamine$_2$ receptors on postganglionic sympathetic nerves and autonomic ganglia inhibits norepinephrine release from sympathetic nerve endings. Thus, the activation of dopamine receptors produces peripheral vasodilatation but does not directly influence contractile function.

Mechanisms of Action of Phosphodiesterase Inhibitors

The inhibition of cardiospecific (FIII) phosphodiesterase is the principal mechanism of action of nonadrenergic inotropic agents such as amrinone, milrinone, and enoximone. Intracellular phosphodiesterases are necessary for cAMP degradation, and their inhibition increases intracellular cAMP concentrations and contractility. Furthermore, the inhibition of phosphoprotein phosphatases, the enzymes required for the dephosphorylation of phosphorylated proteins, produces effects similar to those of increased cAMP. An increased affinity of contractile elements for calcium also enhances contractility; this has been proposed as the principal mode of action of new inotropic agents such as pimobendan and sulmazole.[19]

Mechanism of Action of Glycosidic Inotropic Drugs

The inhibition of surface-bound "sodium pump" is associated with transient increases in intracellular calcium concentrations due to increased sodium influx and activation of the sodium-calcium exchange. This is the proposed mechanism of action of digitalis glycosides.[20]

Systemic Hemodynamic Effects and Changes in Cardiac Performance

Most adrenergic inotropic drugs concurrently stimulate several subtypes of myocardial and peripheral adrenoreceptors, and their net effects are determined by the relative dominance of the receptors stimulated. The activation of myocardial β_1, β_2, and dopamine receptors increases contractility and improves cardiac performance. The stimulation of peripheral β_2 and dopamine receptors is associated with lower systemic vascular resistance and arterial pressure, which decrease left ventricular ejection impedance and improve left ventricular performance. Peripheral vasoconstriction and increased systemic vascular resistance and arterial pressure result from the activation of peripheral α-adrenoreceptors, which also increase left ventricular outflow resistance. Thus, the stimulation of peripheral α-adrenoreceptors may reduce stroke volume and cardiac output and cause deterioration of left ventricular function. Table 2 summarizes the expected systemic hemodynamic effects of newer adrenergic inotropic drugs.

Dopamine and Related Agents

Dopamine hydrochloride and dobutamine hydrochloride. These agents, the two most frequently used parenteral adrenergic inotropic drugs, exhibit some therapeutically relevant differences in hemodynamic effects. In general, each increases cardiac output, but dopamine causes the pulmonary capillary wedge pressure to remain the same or even increase, whereas dobutamine causes it to decrease in most patients.[21] Large doses of dopamine may increase total systemic and pulmonary resistance as well as systemic and pulmonary arterial pressure, thereby increasing the ejection impedance and causing no further increase, or even a decrease, in cardiac output. With dobutamine use, systemic vascular resistance decreases, cardiac output increases, and the mean arterial pressure remains unchanged or even falls. Thus, when the primary objective is to increase arterial pressures in hypotensive patients, the use of dopamine is preferable to that of dobutamine. Using dobutamine is preferable to using dopamine in patients with low cardiac output, adequate arterial pressure, and elevated pulmonary capillary wedge pressure.

Dobutamine therapy also effectively increases systemic output in patients with acute right ventricular failure complicating right ventricular infarction.[22] It has been shown to be more effective than digoxin in improving left ventricular function when given to patients with acute myocardial infarction.[23] When an inotropic agent is necessary for the treatment of acute pump failure, dobutamine is preferable because it acts faster than digoxin.

Newer dopaminergic agents. The systemic hemodynamic effects of newer dopaminergic agents are similar to those of dopamine, but their relative advantages in managing heart failure remain to be established. Dopexamine hydrochloride, an intravenous, short-acting agent, appears to have β_2- and dopamine$_1$-receptor agonist activity. It increases cardiac output and stroke volume while decreasing right atrial and pulmonary capillary wedge pressures.[24] Parenteral propylbutyldopamine has both dopamine$_1$- and dopamine$_2$-receptor agonist activity.[25] Bromocriptine has dopamine$_2$-receptor agonist activity in peripheral vascular beds and decreases sympathetic activity by a central nervous system mechanism.[26] Fenoldopam is a selective dopamine$_1$-receptor agonist.[27]

Ibopamine. This dopamine analogue undergoes hydrolysis to epinine (*N*-methyldopamine) by esterase hydrolase. An orally active drug, it exerts both inotropic and vasodilating effects. Ibopamine appears to activate vascular α_1-adrenoreceptors, β-adrenoreceptors, and dopamine receptors. It increases cardiac output, stroke volume, and stroke work indexes without reflex alterations in heart rate or in mean arterial, systemic, and pulmonary venous pressures. Transient increases in right atrial and pulmonary capillary wedge pressures and in total pulmonary resistance have also been observed.[28]

Levodopa. This pro-drug is converted to dopamine by aromatic amino acid decarboxylase in the liver and other

tissues. Blood concentrations of levodopa and dopamine peak one to three hours after oral administration. Following an oral dose of 1.5 to 2.0 grams of levodopa, systemic hemodynamic effects are similar to those of an infusion of 2.0 to 4.0 μg per kilogram per minute of dopamine. Cardiac output usually increases modestly, without a substantial change in heart rate, blood pressure, or pulmonary capillary wedge pressure, but systemic vascular resistance decreases.[29]

Butopamine. This synthetic sympathomimetic amine is similar to dobutamine except that its resistance to *O*-methylation permits oral administration. Although butopamine exerts a positive inotropic effect, it may produce undesirable, excessive tachycardia.[30]

Denopamine. Another β-receptor agonist, denopamine reportedly produces systemic hemodynamic effects similar to those of butopamine.[31]

Bronchodilators

Albuterol and pirbuterol acetate are primarily β_2-receptor agonists, although they may exhibit ancillary β_1-adrenoreceptor stimulation. The systemic hemodynamic effects of albuterol consist of increased cardiac output, a modestly increased heart rate, and decreased pulmonary capillary wedge pressure and systemic vascular resistance.[32] The systemic hemodynamic effects of pirbuterol are similar to those of albuterol,[33] but undesirable tachycardia has occurred particularly after intravenous administration.

Partial β-Receptor Agonists

A new approach to the inotropic treatment of heart failure has emerged with the development of partial β_1-receptor agonists. These partial agonists cause less than the full physiologic response when all receptors are occupied. On the other hand, full agonists stimulate the full physiologic response when all receptors are occupied, and their physiologic effects are totally inhibited by full antagonists. The pharmacologic rationale for using partial agonists is that their intrinsic sympathomimetic activity exerts a positive but not excessive inotropic effect. Moreover, partial agonists may also attenuate the adverse effects of elevated catecholamine levels.

Prenalterol hydrochloride. This partial β-receptor agonist has 70% to 80% of the sympathomimetic activity of isoprenaline.[34] Prenalterol substantially increases cardiac output and decreases pulmonary capillary wedge pressure and systemic vascular resistance with little or no change in arterial pressure or heart rate.

Xamoterol. In contrast to prenalterol, this selective β_1-receptor agonist has only about 43% of the inotropic and chronotropic activity of isoprenaline. It does not appear to have any significant β_2-adrenoreceptor-agonist activity. Although xamoterol use usually does not produce any immediate beneficial hemodynamic effects in patients with severe heart failure,[35] it does appear to benefit patients with mild to moderate heart failure. The lack of benefit in patients with severe heart failure may relate to the markedly increased sympathetic tone and decreased myocardial β-receptor density usually observed in these patients.

Phosphodiesterase Inhibitors

Although phosphodiesterase inhibitors are structurally dissimilar to each other and to methylxanthines, they exhibit similar pharmacologic properties and systemic hemodynamic effects.[7,36-39] The hemodynamic effects include substantial increases in cardiac output, stroke volume, and stroke work and decreases in systemic and pulmonary venous pressures with little or no change in heart rate or mean arterial pressure. With large doses of phosphodiesterase inhibitors, tachycardia and hypotension may develop.

Positive inotropic effects of phosphodiesterase inhibitors have been documented by various methods. The intra-

TABLE 2.—*Hemodynamic Effects of Selected Adrenergic Inotropic Drugs*

	Receptor Activation			*Hemodynamic Effects*				
Drug	α	β_1	β_2	*SVR*	*Mean BP*	*Cardiac Output*	*Heart Rate*	*PCWP*
Dopamine HCl*	+++	++	–	↓↔	↑↑	↑↑	↑	↑↔
Dobutamine HCl	+	+++	+	↓	↔↓	↑↑↑	↔↑	↓↔
Albuterol	–	+	+++	↓↓	↓↔	↑↑	↔↑	↓↔
Pirbuterol acetate	–	+	+++	↓↓	↓↔	↑↑	↔↑	↓↔
Prenalterol HCl	–	++	–	↓	↔↓	↑	↔↓	↓↔
Xamoterol	–	+	–	↔↓	↔↓	↑	↔↓	↑↔
Levodopa*	+	+	+	↓	↔	↑	↔↑	↔
Ibopamine*	–	+	+	↓	↔	↑	↑↔	↑↔
Dopexamine HCl†	–	+	+	↓	↔	↑	↑↔	↑↔

BP = blood pressure, HCl = hydrochloride, PCWP = pulmonary capillary wedge pressure, SVR = systemic vascular pressure, + = activation, – = no effect, ↑ = increase, ↓ = decrease, ↔ = no change

*Also activates dopamine$_1$ and dopamine$_2$ receptors.
†Acts as a dopamine$_1$-receptor agonist.

TABLE 3.—*Potential Indications for Nonglycosidic Inotropic Therapy*

Intravenous	*Nonparenteral*
Acute heart failure with hypotension	Failure of vasodilators or ACE inhibitors
Acute exacerbation of chronic heart failure with hypotension	Intolerance to vasodilators or ACE inhibitors
In combination with vasodilators	In combination with vasodilators or ACE inhibitors
"Low output state" after a cardiac operation	Refractory heart failure, awaiting cardiac transplantation
Septic shock	
Intermittent infusion in chronic refractory heart failure	

ACE = angiotensin-converting enzyme

coronary infusion of low doses of milrinone did not produce any important systemic hemodynamic effects but did increase left ventricular dp/dt (rate of the rise of pressure), suggesting enhanced contractility.[36] Enoximone, another phosphodiesterase inhibitor but structurally different from milrinone, also exerts direct positive inotropic effects.[37] In addition to enhancing contractility and decreasing afterload, phosphodiesterase inhibitors may improve left ventricular function by increasing left ventricular distensibility.[40] The mechanism for improved left ventricular diastolic compliance, however, remains unclear. Nevertheless, phosphodiesterase inhibitors may enhance cardiac performance by several mechanisms.

Influence of Inotropic Agents on Myocardial Oxygen Consumption

The adrenergic inotropic agents dobutamine and dopamine usually increase myocardial oxygen requirements as well as coronary artery blood flow. Because the increase in blood flow is usually proportional to the increase in myocardial oxygen demand, evidence of myocardial ischemia during inotropic stimulation with dobutamine is relatively uncommon. When tachycardia develops, concurrently compromising left ventricular diastolic perfusion time and increasing myocardial oxygen requirements, abnormal myocardial metabolic function may result. Generally, the more potent β_1-receptor agonists such as dobutamine and dopamine increase myocardial oxygen consumption, whereas the less potent inotropes such as levodopa, xamoterol, and ibopamine may not.

Phosphodiesterase inhibitors appear to induce primary coronary artery vasodilatation as coronary sinus venous oxygen content increases, and myocardial oxygen extraction tends to decrease. Coronary artery blood flow either remains unchanged or increases. The observation that myocardial oxygen consumption frequently does not increase suggests that the coronary artery blood flow continues to exceed metabolic demand.

Clinical Use of Inotropic Agents

Although a large number of adrenergic and nonadrenergic agents are undergoing clinical trials, it is unlikely that any of these agents will be suitable for widespread use, particularly for the management of chronic congestive heart failure. Parenteral inotropic drugs, such as dobutamine and dopamine, and phosphodiesterase inhibitors, such as amrinone, milrinone, and enoximone, will continue to have indications for the short-term treatment of heart failure, as outlined in Table 3. Prolonged parenteral inotropic drug therapy, however, may be associated with worsening heart failure resulting from continued inotropic stimulation. Although intermittent dobutamine or amrinone infusion can provide clinical benefit in some patients with severe chronic heart failure,[41] intermittent parenteral inotropic therapy is indicated only for patients refractory to therapy with vasodilators or angiotensin-converting enzyme inhibitors or for those awaiting cardiac transplantation.

Many nonglycosidic, nonparenteral inotropic agents have undergone numerous clinical trials, but none of these agents have proved to be effective, particularly for producing sustained clinical benefit or improving the prognosis. For example, levodopa therapy produced sustained clinical benefit in some patients with chronic heart failure,[29] but long-term levodopa treatment presents many clinical problems, including drug intolerance and undesirable side effects.

Ibopamine has produced clinical benefit during short-term therapy only.[42] A few preliminary placebo-controlled studies have reported increased exercise tolerance with phosphodiesterase inhibitors such as enoximone and milrinone,[43,44] but these studies had only short-term follow-up and did not show longer survival. Indeed, a trend to higher mortality was observed in patients treated with milrinone.[44] Of all nonparenteral inotropic drugs used for the long-term management of chronic heart failure, digoxin still appears to be the most effective.[44] Thus, the use of new nonparenteral inotropic drugs, when they become available, should be limited to the treatment of specific subsets of patients with congestive heart failure (Table 3).

Summary and Conclusions

Additional controlled studies are required to assess the relative advantages of newer inotropic agents over direct vasodilators or angiotensin-converting enzyme inhibitors, both of which have been shown to decrease mortality substantially. At present, the use of the newer nonglycosidic inotropic drugs should be restricted to specific subsets of patients (Table 3).

Ventricular Arrhythmias

Gary S. Francis, MD*: During the 1970s and well into the 1980s, many short-term studies of vasodilators and positive inotropic agents were conducted in patients with congestive heart failure. Although the principal objective of these studies was to establish the hemodynamic benefits of these agents, a consistent but unreported observation was the high density of complex ventricular arrhythmias, including couplets, multiformed premature ventricular contractions, and nonsustained ventricular tachycardia present in patients with advanced congestive heart failure. Moreover, as the systematic follow-up of patients with heart failure became part of large, multicenter trials, it became apparent that a sizable proportion of patients—about 30% to 40%—die suddenly and unexpectedly, presumably of ventricular arrhythmias.[3] Nearly all patients with symptomatic heart failure have complex ventricular arrhythmias, and 30% to 50% have episodes of nonsustained ventricular tachycardia by Holter monitor.[3] Among the estimated 2 million Americans with congestive heart failure, those with ventricular arrhythmias represent the single largest group at risk for sudden death.

Pathophysiology

The mechanisms of ventricular arrhythmias in patients with congestive heart failure include reentry, abnormal automaticity, and related phenomena after depolarizations and triggered activity. Congestive heart failure is characterized by potentiating conditions that may facilitate arrhythmias. These possible conditions include a combination of myocardial ischemia, mechanical factors, electrolyte imbalance, increased circulating catecholamines, and high basal sympathetic activity, inotropic therapy, or antiarrhythmic therapy.

Myocardial Ischemia

Because a large proportion of patients with congestive heart failure has underlying coronary artery disease, acute

*Associate Professor, Cardiology Section, Department of Veterans Affairs, Minneapolis Medical Center, and University of Minnesota Medical School, Minneapolis.

myocardial ischemia, silent or clinically overt, may be arrhythmogenic in many patients. This concept has important therapeutic implications—it suggests that therapies like nitrates, β-blockers, and coronary artery bypass should be considered for many patients. There is no practical, widely available method to identify heart failure patients at risk of suffering myocardial ischemia and subsequent arrhythmias, however. Ventricular arrhythmias on Holter monitoring in patients with congestive heart failure have not predicted sudden death. Moreover, the potential of anti-ischemic therapy to produce antiarrhythmic effects in patients with heart failure and severe coronary artery disease is unclear. There is little evidence that acute ischemic episodes precipitate life-threatening ventricular arrhythmias in patients with well-established coronary artery disease and heart failure. Most coronary revascularization studies fail to show any lessening of ambient ventricular arrhythmias. It is most likely that the myocardial scar rather than acute ischemia per se is the substrate for most sustained, life-threatening arrhythmias, but without a valid, readily applied method to detect acute ischemic episodes in patients with heart failure, the importance of this potentiating condition remains unknown.

Mechanical Factors

Local mechanical factors in the left ventricle may play a role in the pathogenesis of arrhythmias in heart failure, especially in patients with segmental wall motion abnormalities. The morphology of the electrical signal of the heart can vary according to mechanoelectric feedback. The abnormal mechanics of contraction may initiate an arrhythmia through a close interaction between membrane and mechanical events at the cellular level.[45] For example, mechanically induced electrical changes may modify intracellular calcium, which could affect membrane sodium-calcium exchange[46] and thereby prolong the duration of the action potential. Such mechanical influences occurring late in the cardiac cycle could also change intracellular calcium levels to produce early afterdepolarizations. Given the reduced efficacy of the use of conventional antiarrhythmic drugs in patients with congestive heart failure, mechanoelectric disturbances may be important in generating arrhythmia in this patient population. For patients with symptomatic life-threatening arrhythmias and ventricular aneurysms, the only rational therapy short of heart transplant involves myocardial mapping before and during aneurysmectomy, sometimes combined with a bypass operation, antiarrhythmic drugs, and automatic implantable cardioverter-defibrillators.

Electrolyte Imbalance

The prevalence of electrolyte disturbances in patients with congestive heart failure is well known—hypokalemia and hypomagnesemia are both associated with complex ventricular arrhythmias. A vigorous use of diuretics and high levels of circulating aldosterone also contribute to these disturbances. Studies by Dargie and colleagues indicate an important inverse relationship between serum potassium levels and ventricular arrhythmias in these patients.[47] The influence of supplemental potassium on ventricular arrhythmias has not been systematically studied in patients with congestive heart failure, but a reasonable approach would be to maintain serum potassium levels in the high to normal range, 4 to 5 mmol per liter. The angiotensin-converting enzyme inhibitors captopril and enalapril, which maintain or increase serum potassium levels by inhibiting the renin-angiotensin-aldosterone system, have reduced ventricular arrhythmia density in some patients with congestive heart failure.[48,49]

Sympathetic Activity

Sympathetic nervous system activity, measured directly by neurographic techniques or indirectly by plasma norepinephrine levels,[50] is increased in patients with congestive heart failure.[51] There is a clear association between circulating plasma norepinephrine levels and mortality[52] and a significant relation between premature ventricular contraction density and plasma norepinephrine levels[47] in patients with congestive heart failure. β-Adrenergic blockers have improved function in selected patients with dilated cardiomyopathy, and administering angiotensin-converting enzyme inhibitors has produced short-term reductions in plasma norepinephrine levels and ventricular arrhythmias, along with improved survival, in patients with class IV congestive heart failure.[5] Together these data suggest that excessive sympathetic drive may contribute to the poor survival rate of patients with congestive heart failure and that treatment to reduce sympathetic activity may be beneficial, perhaps in part through an antiarrhythmic effect.

Inotropic Therapy

Under certain conditions, inotropic therapy, including digitalis, has a well-known proarrhythmic effect. All positive inotropic agents have the potential to enhance arrhythmias by inducing acute myocardial ischemia and by direct effects on transmembrane potential. Large doses of dopamine[53] and dobutamine[54] are clearly arrhythmogenic, and digitalis was retrospectively implicated in the lower survival of patients who had sustained a myocardial infarction.[55] There are, however, no prospective data on the influence of digitalis on survival,[56] and digitalis remains a widely used agent to treat congestive heart failure. The National Institutes of Health and the Department of Veterans Affairs are planning a multicenter, prospective, placebo-controlled trial to study the influence of digitalis on survival in patients with congestive heart failure. Until more data are available from this and similar trials, all positive inotropic agents, including digitalis, should be considered potentially arrhythmogenic in these patients.

Antiarrhythmic Therapy

Another possible cause of life-threatening arrhythmias in patients with congestive heart failure may be antiarrhythmic therapy itself. In the Vasodilator-Heart Failure Trial, the use of antiarrhythmic therapy was a significant risk factor for shortened survival in patients with heart failure.[57] Because there was no intent to control for antiarrhythmic therapy in this trial, we cannot know if the increased mortality resulted from antiarrhythmic therapy or from inherent selection bias.

Antiarrhythmic therapy is generally thought to carry a 10% to 15% risk of proarrhythmia, depending on how that term is defined.[58] In patients with advanced congestive heart failure, proarrhythmic risk may be even higher. Side-effect profiles for antiarrhythmic drugs may also be more prominent in these patients, a finding that may relate to greatly altered pharmacokinetics and pharmacodynamics.[59] In addition, patients with severe left ventricular dysfunction (ejection fraction of <35%) seem less responsive to antiarrhythmic agents.[60] One small uncontrolled trial showed no

difference in survival when 43 patients with severe heart failure were followed during two years of treatment with a type IA antiarrhythmic drug versus no antiarrhythmic therapy.[9] Thus, left ventricular dysfunction rather than the pharmacologic control of ventricular arrhythmias may be the driving force behind the high mortality rate in patients with heart failure.[61] Because of the risks of drug-aggravated arrhythmias, heightened side effects, enhanced myocardial depression, and general ineffectiveness, the empiric use of type I antiarrhythmic drugs in patients with asymptomatic ventricular arrhythmias and heart failure is not recommended.

Management

The consensus is that patients with heart failure and symptomatic ventricular tachyarrhythmias should be treated following incidents such as a cardiac arrest or an episode of sustained ventricular tachycardia with lightheadedness. Some consider electrophysiologic testing to be of value in patients with symptomatic arrhythmias,[62] particularly in those with ischemic heart disease. A combination of exercise testing, Holter monitoring, and electrophysiologic testing has been used to determine the effectiveness of combination therapy, including giving amiodarone and β-blockers.[63] Signal-averaged electrocardiograms may also be useful in identifying patients at risk for sudden death. No uniformly accepted protocol exists, however, to assess antiarrhythmic drug efficacy in treating symptomatic ventricular arrhythmias in patients with heart failure. Nevertheless, the best approach is to undertake treatment while patients are in hospital and monitored by continuous electrocardiography.[64] Comprehensive treatment should always include maintaining an optimal electrolyte balance and hemodynamic status. In contrast to the general agreement about the treatment of symptomatic ventricular tachyarrhythmias, substantial controversy continues about the treatment of asymptomatic ventricular tachyarrhythmias in patients with heart failure.[65] Electrophysiologic testing in these patients, especially in those with primary dilated cardiomyopathy, is of limited value.[66]

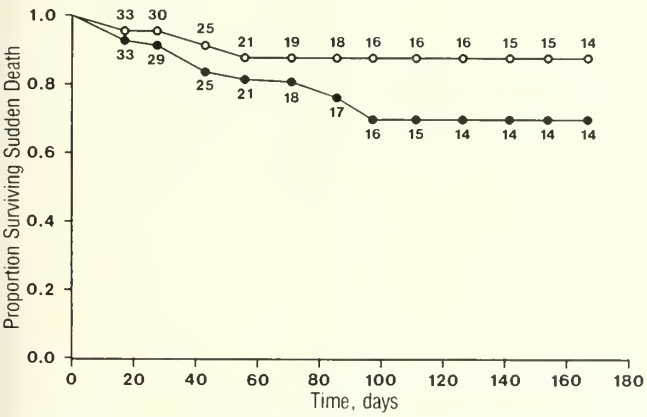

Figure 1.—Cumulative rates of survival without sudden death were compared for patients who received no antiarrhythmic therapy **(closed circles)** and patients who received quinidine, procainamide, or amiodarone **(open circles).** The numbers represent study participants available for follow-up (from Simonton et al[67]).

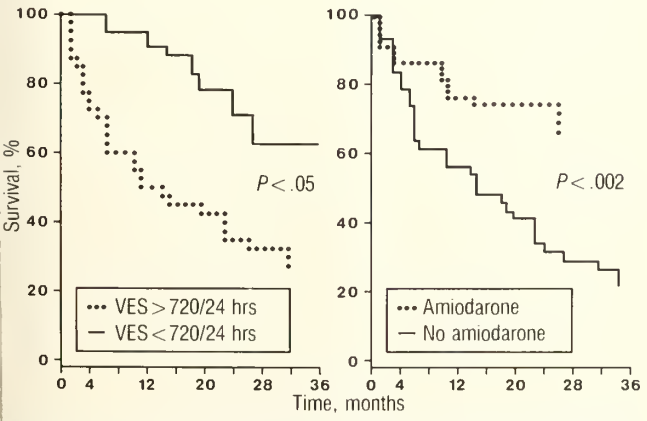

Figure 2.—A Kaplan-Meier analysis shows the influence of ventricular extrasystoles (VES) and the administration of amiodarone on the survival of 84 patients with chronic heart failure (from Cleland et al[48]).

Several small, uncontrolled trials have evaluated empiric antiarrhythmic drug therapy in patients with congestive heart failure. An uncontrolled study by Simonton and co-workers found that antiarrhythmic therapy decreased the frequency of sudden death in 82 patients treated with phosphodiesterase inhibitors (Figure 1).[67] Of these patients, 43 received no antiarrhythmic therapy, and the others received quinidine, procainamide, or amiodarone. At six months, sudden death had occurred in 29% of patients not receiving antiarrhythmic therapy and in only 13% of patients receiving antiarrhythmic drugs. Similar results were reported by Neri and associates, who noted dramatically reduced premature ventricular contractions in more than 70% of patients with congestive heart failure treated with amiodarone for three years.[68] In a prospective crossover study, Cleland and colleagues also found that small doses of amiodarone (mean dose, 183 mg per day) greatly reduced the frequency of life-threatening ventricular arrhythmias and the overall mortality rate among patients with severe heart failure (Figure 2). A recently reported randomized, placebo-controlled trial of amiodarone in patients with severe heart failure failed to show any benefit to drug-treated patients.[69]

Although some of these studies were not randomized (and thus were subject to selection bias)[48,67,68] and may have been too small to measure statistically significant effects on mortality,[69] they are important because they suggest that amiodarone can suppress ventricular arrhythmias,[48,67,68] and its use may be reasonably well tolerated[69] by patients with advanced congestive heart failure. Moreover, they bring into focus a testable hypothesis: Antiarrhythmic drug therapy may improve survival in patients with congestive heart failure. Data are as yet insufficient to recommend antiarrhythmic drug therapy to prolong the survival of patients with asymptomatic ventricular arrhythmia.

Summary and Conclusions

Life-threatening ventricular arrhythmias are common in patients with congestive heart failure, and about 30% to 40% of these patients die suddenly. Many mechanisms are probably involved in the pathogenesis of these arrhythmias; therefore, no single therapy is likely to be effective. Symptomatic ventricular arrhythmias should be treated; such therapy might include more than one antiarrhythmic agent, surgical therapy, and automatic implantable cardioverter-defibrillators. The role of antiarrhythmic drug therapy for asymptomatic ventricular arrhythmias in patients with heart failure remains uncertain, but preliminary studies suggest that amiodarone may be useful. The Department of Veterans Affairs has recently begun a randomized, placebo-controlled trial to test the hypothesis that the use of amiodarone may

prolong survival in patients with chronic congestive heart failure.

Ventricular Remodeling After Myocardial Infarction

BRIAN G. FIRTH, MD, DPhil*: Coronary atherosclerosis with resultant myocardial infarction is the most important single cause of heart failure in the United States today. After a first acute myocardial infarction, overt heart failure develops in only a minority of patients, but 14% of these patients will have heart failure within five years and 22% within ten years.[70] Late heart failure may result from further myocardial infarction, with a further loss of functional myocardium, or from dilatation and remodeling of the heart.

The amount of irreversibly damaged myocardium after one or more infarctions is the single greatest determinant of long-term survival.[71] Although the left ventricular ejection fraction has been widely used as a postinfarction index of residual myocardial function, Hammermeister and associates suggested ten years ago that the left ventricular volume may be a more sensitive predictor of outcome than the ejection fraction.[72] Recent work by White and colleagues supported this notion with the demonstration that, although the left ventricular ejection fraction is an important predictor of postinfarction survival, patients with larger end-systolic volumes at any given ejection fraction have a worse prognosis over eight years than those with smaller volumes.[73] Thus, the degree of left ventricular dilatation and remodeling following myocardial infarction appears to be of cardinal importance.

Pathophysiology of Dilatation

Klein, Herman, and Gorlin determined that the stroke volume could not be maintained without ventricular dilatation if more than 20% of the ventricular wall is destroyed.[74] Kitamura and co-workers also drew attention to "the geometric and functional abnormalities of the left ventricle" that occur "with a chronic localized noncontractile area."[75] Investigators at Johns Hopkins Medical School (Baltimore, Md) later attempted to define more precisely the consequences of localized myocardial damage by doing a series of important studies in humans and in a rat model of myocardial infarction.

Hutchins and Bulkley performed autopsies on 76 consecutive patients who died within 30 days after an acute myocardial infarction.[76] Infarct extension—histologically more recent foci of contraction-band necrosis around an infarct—was noted in 13 autopsies (17%). Infarct expansion, however—acute dilatation and thinning of the infarct area not explained by additional myocardial necrosis—was seen in 45 autopsies (59%). Severe infarct expansion did not develop until five days after infarction and was greater with first and transmural anterior infarcts.

In a subsequent study, Eaton and associates performed serial two-dimensional echocardiographic studies of 28 patients within 14 days of acute infarction.[77] They observed a progressive increase in infarct-segment length in 8 patients, whom they designated as "expanders," but essentially no change in infarct-segment length in the other 20. Again, infarct expansion occurred predominantly in those with large anterior or anteroseptal transmural infarcts. Expansion was detected by 3 days after infarction and appeared to continue for at least the first 14 days. In this study, the authors suggested that dilatation and expansion involved only the infarct region. A subsequent study by this group found lengthening of both the infarcted and uninfarcted segments extended for 3 to 30 months after infarction in 13 patients with transmural anterior myocardial infarction.[78] Of the 13 patients, 7 showed evidence of infarct expansion by two-dimensional echocardiography, and the segmental dilatation rate averaged 1 mm per month for both infarcted anterior wall and uninfarcted posterior wall segments. Thus, left ventricular dilatation seems to involve a stretching of both the infarcted and uninfarcted myocardial segments.

The Johns Hopkins investigators did further studies of postinfarction myocardial remodeling in rats.[79] Transmural infarcts were produced in 45 rats by ligating the left coronary artery; rats were killed on days 1, 2, and 3 after infarction. (In rats, ligating the left coronary artery does not produce septal infarction, and histopathologic changes, myocardial thinning, dilatation, and remodeling occur about twice as rapidly as in humans.) Of the 45 rats, infarct expansion developed in 28. The 17 without infarct expansion had a mean infarct size of 22% $\pm$ 2% of left ventricular mass, which was significantly smaller than that of the 28 with infarct expansion: Mean infarct size as a percentage of left ventricular mass was 35% $\pm$ 4% for those with 1+, 42% $\pm$ 5% for those with 2+, and 45% $\pm$ 5% for those with 3+ to 4+ expansion. Thus, infarct size does appear to have a bearing on infarct expansion, but, beyond a certain size, other factors may determine the severity of expansion. In rats showing evidence of expansion, wall thickness decreased 55% in the infarct zone and 28% in the remote uninfarcted region. This confirmed that the uninfarcted myocardium is intimately involved in the postinfarction dilatation process.

Factors That May Affect Dilatation

Because the infarct size does not appear to be the sole determinant of the severity of infarct expansion after myocardial infarction, Nolan and colleagues investigated the effect of increased afterload on this process.[80] In that study, 40 rats were randomly assigned to aortic banding (n = 20) or a sham operation (n = 20) and allowed to recover for three weeks. They were then randomly assigned to left coronary artery ligation (n = 30) or a sham operation (n = 10). Rats were killed seven days later, and morphologic changes in the myocardium were characterized. Although infarct size as a percentage of left ventricular mass was smaller at death in rats with aortic banding, infarct expansion as measured by cavity dilatation and infarct thinning occurred in both groups but was greater in rats with aortic banding.

The extent to which increased afterload per se, as opposed to a resultant myocardial hypertrophy, was responsible for these effects is uncertain. It is also uncertain how the observed effects of a short-term increase in afterload relate to those of chronic systemic arterial hypertension, their clinical counterpart. Nevertheless, the rat study results seem to be consistent with the observation that myocardial rupture as a sequela of infarct thinning and expansion is more common in patients with systemic arterial hypertension.[81] This study also included the important observation that hypertrophy of uninfarcted myocardium occurred in response to myocardial infarction.[80] Recent evidence suggests that such hypertrophy may be pathologic because it may be associated with a change

*Associate Professor, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas. Dr Firth is now with E.R. Squibb & Sons, Princeton, NJ.

n myosin isoform from V_1 to V_3 and with a localized, depressed coronary artery vasodilator reserve.[82]

Various other factors may contribute to left ventricular dysfunction after infarction. These include variable collagen ngrowth into the infarcted region, subendocardial ischemia, cellular calcium overload, catecholamine toxicity, decreased β-receptor regulation, a reduced amount of myocardial stimulatory guanine nucleotide regulatory protein, dyssynchronous contraction, and interaction between right and left ventricles. In addition, the use of certain drugs, including corticosteroids and nonsteroidal anti-inflammatory agents, may aggravate this process.[83]

Left Ventricular Dilatation in Humans

Recent studies in humans not only confirm many of the observations in rats but also consider the possible role of infarct-related artery patency in preventing or ameliorating left ventricular dilatation. McKay and co-workers did coronary angiography and left ventriculography within the first few hours of infarction and again at 14 days in 30 patients who received thrombolytic therapy.[84] The only patients included in their report were those who showed early improved flow in the infarct-related artery. Despite this, left ventricular end-systolic and end-diastolic volume indices increased significantly ($P < .01$) in the group as a whole at two weeks. The increase in the left ventricular end-diastolic volume index correlated directly ($r = .71$, $P < .001$) with infarct size, measured as the percentage of the ventriculographic silhouette that was akinetic or dyskinetic at the initial catheterization. The mean endocardial-perimeter length increased 13% in infarcted segments and 19% in uninfarcted segments. At the same time, decreased left ventricular filling pressures and increased cardiac output occurred at the expense of a substantial increase in ventricular chamber volumes.

These investigators also studied the time course of left ventricular dilatation in 36 patients, with serial radionuclide ventriculograms taken at 1 and 11 days and at 10½ months after acute transmural myocardial infarction.[85] In 20 of the 36 patients, the left ventricular volume increased more than 20%. Left ventricular dilatation was more frequent and chronic dilatation significantly more pronounced ($P < .01$) in patients with left anterior descending as opposed to right coronary artery occlusion (Figure 3). These investigators could not discern a difference in left ventricular volumes or ejection fraction among patients with successful versus unsuccessful thrombolysis at four to six hours.

Jeremy and associates also evaluated the effect of infarct artery patency on subsequent changes in ventricular volume and came to a diametrically opposite conclusion.[86] In their study of 40 patients who did not receive thrombolytic therapy, infarct artery perfusion was documented by predischarge coronary angiography, and left ventricular volumes were measured at 48 hours and 1 month after a first acute myocardial infarction. By multiple linear regression analysis, the degree of perfusion of the infarct artery ($r = .58$, $P = .001$) was a more important predictor of volume change than was infarct size measured by peak creatine kinase levels ($r = .30$, $P = .009$). Left ventricular dilatation—an increase of 20% or more in volume—occurred in all 14 patients who did not have perfusion of the infarct-related artery but in only 2 of the 26 patients who had perfusion of this artery due to subtotal occlusion or collateral vessels. The importance of perfusion of the infarct-related artery and the time at which it should occur to limit left ventricular dilatation remain matters of considerable debate.

Effects on Dilatation of Therapy With Angiotensin-Converting Enzyme Inhibitors

Although many factors may affect ventricular dilatation and remodeling, it seems likely that increased wall stress is among the most important. Pfeffer and colleagues tested this hypothesis in a rat model of myocardial infarction.[87] At 2 or 21 days following left coronary artery ligation, 104 rats were randomly assigned to treatment with standard drinking water or with the angiotensin-converting enzyme inhibitor captopril in standard drinking water. After three months of this regimen, hemodynamic measurements were made before and during volume loading experiments, and then the animals were killed. Although infarct size as a percentage of left ventricular mass did not differ between the groups, left ventricular end-diastolic pressure was significantly lower ($P < .01$) in captopril-treated rats with small, moderate, or large infarcts. In response to volume loading, captopril-treated rats had higher peak stroke volumes and lower left ventricular volumes than control animals. Finally, captopril treatment improved relationships between diastolic pressure and volume, allowing infarcted hearts to function at smaller volumes and lower left ventricular filling pressures.

The same laboratory conducted a later placebo-controlled study of 302 rats with myocardial infarction to determine effects on one-year survival of administering captopril beginning on day 14 after an infarction.[88] As expected, survival was directly related to infarct size in placebo-treated rats. Overall survival was significantly greater ($P < .02$) in the captopril-treated group, however, with the most pronounced benefit occurring in rats with moderate-sized infarcts. This improved survival also appeared to be related to the attenuation of ventricular dilatation.

Finally, this group did a pilot study in 59 patients to assess the efficacy of prophylactic treatment with an angiotensin-converting enzyme inhibitor after a first anterior transmural myocardial infarction.[89] Patients, all of whom had left ventricular ejection fractions of 45% or lower and no overt heart failure, underwent cardiac catheterization approximately 18 days after infarction and were randomly assigned to captopril or placebo treatment for a year. Captopril was discontinued 20 hours before catheterization at one year. At this time, significant decreases from baseline values were observed in left ventricular end-diastolic pressure ($P < .005$), pulmo-

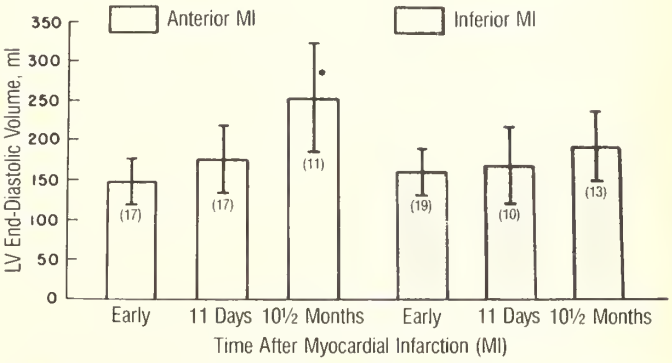

Figure 3.—Left ventricular (LV) end-diastolic volume after myocardial infarction was measured in patients with anterior versus inferior infarction. Asterisk indicates $P < .01$ for anterior MI versus inferior MI at 10½ months. Numbers in parentheses are the number of patients (from Warren et al[85]).

nary capillary wedge pressure ($P < .01$), and mean pulmonary artery pressure ($P = .05$) in captopril-treated but not in placebo-treated patients. Conversely, left ventricular end-diastolic volume increased significantly ($P < .02$) in placebo-treated but not in captopril-treated patients. Intergroup analyses for these variables did not achieve statistical significance, however.

These preliminary results showed that the two most important predictors of ventricular dilatation were persistent occlusion of the infarct-related artery at baseline catheterization and the extent of wall-motion abnormality, defined as akinesis plus dyskinesis of 30% or more of the diastolic perimeter at baseline. The greatest benefit of treatment with the angiotensin-converting enzyme inhibitor was seen in those with a closed infarct-related artery and akinesis plus dyskinesis of more than 30% (Figure 4). Another recent study by Sharpe and colleagues evaluated 60 patients after acute myocardial infarction.[90] Their observations also supported the conclusion that treatment with angiotensin-converting enzyme inhibitor may have a beneficial effect on left ventricular dilatation and remodeling.

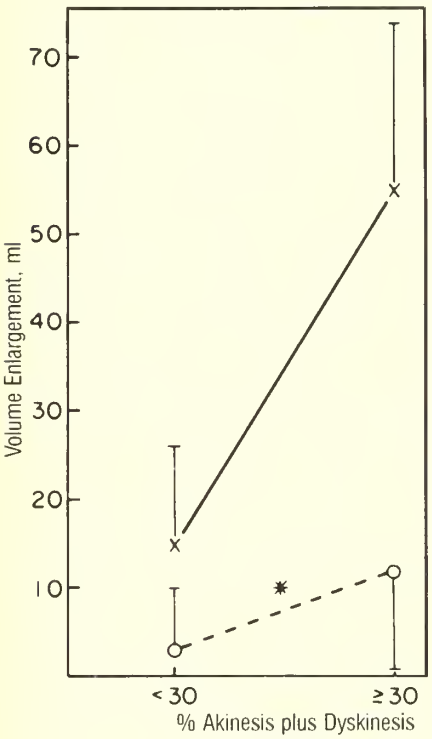

Figure 4.—An increase in left ventricular end-diastolic volume (volume enlargement) is shown in patients with occlusion of the left anterior descending coronary artery at baseline catheterization (n = 36). The dotted line represents the values for patients receiving captopril, the solid line those receiving placebo. The asterisk denotes significance at $P < .05$ (from Pfeffer et al[89]).

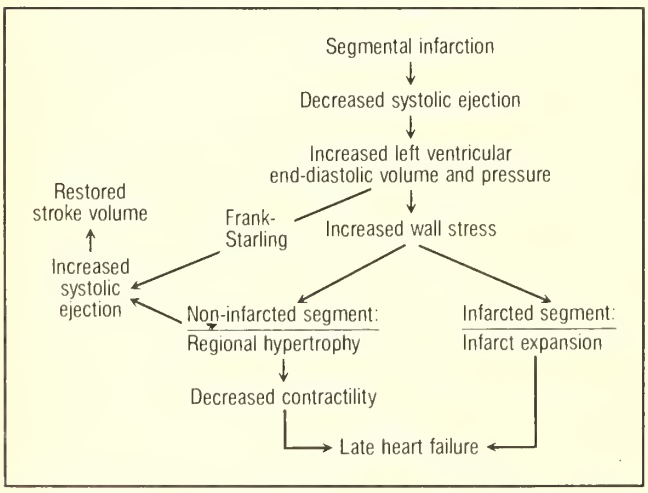

Figure 5.—The schematic represents the hypothesis proposed to account for mechanisms of left ventricular remodeling (from McCay et al[84]).

Summary and Conclusions

Although studies in animals and humans suggest that treatment with angiotensin-converting enzyme inhibitors may be beneficial, such data should be regarded as preliminary until results of the much larger Survival and Ventricular Enlargement (SAVE) and Studies of Left Ventricular Dysfunction (SOLVD) trials become available. McKay and associates have presented a useful hypothesis to explain the sequence of events that causes segmental left ventricular dysfunction to result in increased wall stress and ultimately in left ventricular dilatation, remodeling, and overt heart failure (Figure 5).[84] Conceivably, angiotensin-converting enzyme inhibitors may attenuate left ventricular dilatation by unique properties such as abolishing the toxic effects of angiotensin II on myocardium or mitigating the effects of reduced myocardial stimulatory guanine nucleotide regulatory protein. It seems more likely, however, that effects of these drugs on dilatation relate to reducing systolic and diastolic wall stress without an accompanying reflex increase in catecholamines during the remodeling period.

It is worth recalling that β-blockers appear to reduce all causes of postinfarction mortality, including myocardial rupture and progression to congestive heart failure.[91] Thus, overlapping benefits may accrue from a combined use of angiotensin-converting enzyme inhibitors and β-blockers. Even earlier intervention with such agents, aimed at limiting infarct size and reducing wall tension as soon as possible after infarction, may have an even more salutary effect on left ventricular dilatation than when postinfarction treatment begins within days to weeks.[92] Further studies will be needed to answer these questions definitively and to determine possible incremental benefits of such therapy in conjunction with thrombolytic therapy or emergency angioplasty for acute myocardial infarction.

One conclusion seems clear: To make a serious impact on the escalating mortality from congestive heart failure, we will need to intervene much earlier. This implies not only preventing left ventricular dilatation and remodeling but also limiting myocardial infarct size and attempting to reduce the incidence of infarction by dealing more effectively with well-recognized risk factors such as cigarette smoking, hyperlipidemia, and hypertension.

Adjuvant Therapy for Coronary Reperfusion—Role of Oxygen-Radical Scavengers?

ROBERT A. KLONER, MD, PhD, in collaboration with KARIN PRZYKLENK, MD*: In the past, the fate of ischemic myocardium was thought to be determined primarily by the imbalance between oxygen supply and demand. Interventions aimed at reducing myocardial ischemic injury either enhanced oxygen supply (usually by increasing coronary blood flow or coronary collateral flow) or reduced oxygen demand (usually by decreasing the heart rate, afterload, or contractility). Recent evidence suggests, however, that myocardial in-

*The Heart Institute of the Hospital of the Good Samaritan and the Division of Cardiology, University of Southern California School of Medicine, Los Angeles.

jury may be exacerbated by cytotoxic, oxygen-derived free radicals generated during ischemia or reperfusion. This oxygen-radical theory of ischemic and reperfusion injury raised the potential for new therapies to attempt to blunt myocardial damage by scavenging these reactive oxygen species. In this section we will discuss coronary artery reperfusion as a complex phenomenon with both beneficial and potentially deleterious consequences; the oxygen-radical theory of tissue injury; pharmacologic adjuvant therapy for acute myocardial infarction and stunned myocardium; and the possible role of agents such as calcium-channel blockers, β-blockers, and oxygen-radical scavengers.

Coronary Artery Reperfusion Phenomena

Beneficial Effects of Early and Late Reperfusion

Coronary artery perfusion after acute myocardial infarction unquestionably has beneficial effects[93]: Timely reperfusion has been shown to limit myocardial infarct size,[94] to improve left ventricular function,[95] and to enhance survival.[96] Although early reperfusion—within three to four hours of the start of ischemia—is most likely to salvage ischemic myocardium, our laboratory and others have also observed benefits of late coronary artery reperfusion in experiments in animals.

Delayed reperfusion did not reduce infarct size or salvage previously ischemic myocardium, but it did produce a thicker infarct scar and reduce myocardial infarct expansion.[97] In addition, late coronary reperfusion appeared to have beneficial effects on ventricular arrhythmias, as assessed by ambulatory electrocardiographic monitoring four days after coronary artery occlusion.[98] Reperfusion six hours after occlusion reduced the total runs of ventricular tachycardia as well as the frequency of runs of greater than 200 beats per minute and of runs longer than 60 seconds. Finally, late reperfusion resulted in a patent, infarct-related coronary artery, which may serve as both a source of coronary collateral blood flow to other jeopardized areas of the heart and a route by which pharmacologic agents such as antiarrhythmics can penetrate peri-infarct tissue. The beneficial effects of delayed reperfusion may in part explain the reduced mortality observed in patients receiving thrombolytic therapy as late as 13 to 24 hours after symptoms began in the Second International Study of Infarct Survival (ISIS-2) trial[99] and the reduced mortality without reduced infarct size observed in the western Washington trial.[100]

Potentially Deleterious Effects of Reperfusion

The potentially deleterious consequences of reperfusion have been reviewed in detail previously[93] and include explosive cell swelling, hemorrhagic myocardial infarction, the no-reflow phenomenon, "stunned myocardium," "reperfusion injury," and ventricular arrhythmias. Cytotoxic oxygen radicals, formed during ischemia and reperfusion, are thought to play an important role in some of these deleterious effects, including stunned myocardium, reperfusion injury, no-reflow, and reperfusion arrhythmias.[101]

Oxygen-Radical Theory of Tissue Injury

A free radical is a molecule with an odd, unpaired electron. This unpaired electron makes the molecule unstable and highly reactive. Reactive oxygen species thought to be generated during ischemia and reperfusion—the superoxide anion, the hydroxyl radical, and their intermediary hydrogen peroxide—can result in lipid peroxidation of membranes and denaturation of proteins. Such damage can impair cell-membrane permeability, lead to altered function of myocardial cellular organelles including sarcoplasmic reticulum, and possibly result in cell death.[102] Exposure of the myocardium to oxygen radicals can result in myocyte injury[103] and depressed cardiac function.[104]

Evidence from these in vitro and in vivo experiments suggests that oxygen-centered radicals may be generated during ischemia and reperfusion. Oxygen radicals have been detected in the myocardium and coronary effluent of hearts subjected to transient ischemia.[105] Other investigators have documented depletion of the normal, endogenous enzymatic defenses against free-radical injury following transient ischemic episodes, suggesting that oxygen free radicals may have been present in the myocardium during ischemia and reperfusion. Potential sources for the generation of oxygen radicals during ischemia and reperfusion include the xanthine oxidase reaction,[106] although this reaction is species dependent[107]; activated neutrophils[108,109]; mitochondria[110]; and arachidonic acid metabolism.

Adjuvant Therapy for Acute Myocardial Infarction—A Potential Role for Oxygen-derived Free-Radical Scavengers?

Adjuvant therapy for acute myocardial infarction refers to the administration of pharmacologic agents along with thrombolytic therapy or angioplasty to further improve outcome. Acute adjuvant pharmacologic therapy could improve the function of the heart by enhancing the recovery of stunned myocardium (postischemic dysfunction of viable, reperfused myocytes); increase the "window in time" in which reperfusion effectively reduces myocardial infarct size so the adjuvant agent plus reperfusion would reduce infarct size more than reperfusion alone; maintain vessel patency following thrombolysis, thereby reducing the incidence of reocclusion; and reduce or prevent reperfusion arrhythmias. We will discuss adjuvant therapy for stunned myocardium and reperfused infarction as well as the possible role of adjuvant agents, such as calcium blockers, β-blockers, and oxygen-radical scavengers, administered during the acute phase of ischemia and reperfusion.

Adjuvant Therapy for Stunned Myocardium

The term "stunned myocardium" refers to viable myocardium, salvaged by reperfusion, in which there is prolonged but reversible postischemic contractile dysfunction.[111] This phenomenon was first described following 15 minutes of coronary artery occlusion in dogs. This ischemic period did not cause myocyte death but did cause abnormal regional contractile function in salvaged tissue, an effect that persisted for hours to days after reperfusion.[111] This myocardial dysfunction occurred after prolonged transient coronary artery occlusion—a subendocardial infarct was produced in two hours. In this instance, however, subepicardial tissue salvaged by reperfusion remained stunned for days to weeks after reflow.[111]

Considerable experimental evidence suggests that oxygen-derived free radicals play a role in the pathogenesis of stunned myocardium. This hypothesis is supported by several studies in which potent free radical-scavenging enzymes, superoxide dismutase plus catalase, were administered preceding 15 minutes of coronary artery occlusion in

anesthetized open-chest dogs. Pretreatment with the scavenging agents consistently enhanced regional contractile function of stunned, postischemic tissue during the initial two to three hours after reflow compared with that of controls pretreated with a saline solution.[112] Similar beneficial results were more recently obtained with other free-radical scavengers, as reviewed by Bolli.[113] Antioxidants, iron chelators, quenching agents, and spin traps[105,113] have all been shown to improve contractile function of postischemic, stunned myocardium in the canine model.

There is little doubt that oxygen free radicals contribute to the phenomenon of stunned myocardium, but sources of these free radicals—the xanthine oxidase reaction,[106,107] activated neutrophils,[108,109] the mitochondrial electron transport chain,[110] or arachidonic acid metabolism—in these models of brief, transient ischemia remain speculative. For example, Engler and Covell reported that the virtual elimination of neutrophils by leukocyte filtration ablated postischemic contractile dysfunction produced by 15 minutes of coronary artery occlusion in anesthetized dogs.[114] In contrast, other investigators failed to document any beneficial effect of neutrophil filtration[115] or suppression[116] on the recovery of regional contractile function in dogs. Furthermore, both our laboratory[117] and others[118] have found that transient coronary artery occlusion does not appear to be associated with neutrophil infiltration. Thus, the importance of neutrophils in the pathogenesis of stunned myocardium in models of brief ischemia is questionable. Two- to three-hour periods of ischemia causing myocardial cell death have been associated with neutrophil influx following reperfusion, however[108]; thus, neutrophils could contribute pathogenically to the phenomenon of stunned myocardium in the peri-infarct zones.

It should be noted that all agents that scavenged, quenched, or otherwise inhibited free-radical production restored the contractile function of stunned myocardium to a maximum of only 50% to 70% of baseline preocclusion values.[112] These data suggest that other mechanisms—including abnormalities in calcium metabolism, abnormal energy transduction, and the low-reflow phenomenon—may also be important causes or mechanisms of postischemic contractile dysfunction. Several recent studies suggest that alterations of calcium flux may contribute to the phenomenon of stunned myocardium. Intravenous nifedipine administered 30 minutes after reperfusion[119] in anesthetized dogs virtually ablated stunned myocardium. The parenteral administration of nifedipine may have enhanced the return of function of stunned myocardium by reducing afterload or increasing postreperfusion myocardial blood flow. A minute intracoronary dose of nifedipine, however, which did not alter hemodynamics or regional myocardial blood flow, also restored the function of stunned myocardium, suggesting that the drug had a direct effect on myocardial cells.[119] The treatment of stunned myocardium with verapamil—before occlusion, at reflow, or 30 minutes after reperfusion—also enhanced the return of function.[120]

Could there be a connection between the beneficial effects of oxygen-derived free-radical scavengers and calcium blockers? Theoretically, these two seemingly diverse mechanisms may be interrelated. Oxygen free radicals generated during ischemia and reperfusion can cause lipid peroxidation of cell membranes. Damaged membranes could make myocardial cells more susceptible to alterations in calcium flux. These alterations might include not only the influx of calcium into cells but also fluxes of calcium within intracellular pools—between the sarcoplasmic reticulum and actin-myosin filaments. In addition, the conversion of xanthine dehydrogenase to xanthine oxidase (important in the ultimate generation of superoxide radicals) is thought to be mediated by calcium-dependent proteases. Thus, these hypothetical links between oxygen radicals and alterations in calcium flux may play a role in the pathogenesis of stunned myocardium.

Other adjuvant therapies have been explored in models of stunned myocardium. The use of angiotensin-converting enzyme inhibitors and afterload reducers like hydralazine have improved the function of stunned myocardium.[121]

Adjuvant Therapy to Reduce Myocardial Infarct Size

Timely coronary artery reperfusion unquestionably reduces myocardial infarct size, but whether adjuvant pharmacologic therapy can reduce infarct size more than reperfusion alone remains controversial. Various types of pharmacologic agents have been tested as adjuvants. In some studies, administering pharmacologic therapy during both ischemia and reperfusion was shown to be of benefit. In anesthetized dogs, Reimer and Jennings observed that administering verapamil preceding a 40-minute coronary artery occlusion plus reperfusion reduced infarct size more than reperfusion alone.[122] With the duration of ischemia extended to three hours, however, the beneficial effect of the calcium blocker was lost. Similarly, our laboratory reported that the intracoronary administration of verapamil did not reduce infarct size more than reperfusion alone.[123]

Some studies have suggested that β-blockers combined with reperfusion may further limit myocardial infarct size. Hammerman and co-workers showed that administering timolol during a three-hour experimental coronary artery occlusion followed by reperfusion reduced myocardial infarct size.[124] Studies in other experimental models, however, suggested that the use of propranolol did not reduce myocardial infarct size.[125] A potential mechanism of both calcium and β-blockers in these models is reducing oxygen demand during ischemia.

Certain forms of adjuvant therapy have been shown in large clinical trials to be beneficial. For example, in the ISIS-2 collaborative group trial, the combination of streptokinase with aspirin reduced the incidence of vascular deaths due to suspected acute myocardial infarction more than the use of either agent alone.[99] Aspirin therapy also reduced the incidence of nonfatal reinfarction that was observed with using streptokinase alone. In the Phase II Thrombolysis in Myocardial Infarction trial, the combination of tissue plasminogen activator plus early metoprolol therapy reduced the incidence of nonfatal reinfarction and recurrent ischemic episodes.[126] Data on the role of calcium blockers in patients receiving thrombolytic therapy are limited. In patients without thrombolysis, calcium blockers have generally not reduced infarct size or prolonged survival. Some have been shown to reduce the severity of postinfarct angina pectoris and possibly to reduce the incidence of reinfarction after non-Q-wave infarction. Table 4 lists possible forms of adjuvant pharmacologic therapy for acute myocardial infarction.

Oxygen-derived Free Radicals and Reperfusion Injury

Investigators have postulated that oxygen-derived free-radical scavengers might serve as useful adjuvant therapy for acute myocardial infarction.[127] This concept is based on the

TABLE 4.—*Initial Adjuvant Agents Used With Thrombolytic Therapy for Acute Myocardial Infarction*

Agent	*Comment*
Aspirin	In the ISIS-2 trial, aspirin therapy improved survival and reduced nonfatal reinfarction; other antiplatelet agents are being investigated
β-Blockers	In the TIMI II trial, early metoprolol administration reduced the incidence of nonfatal reinfarction and recurrent ischemia; effects of β-blockers on experimental infarct size in reperfusion models have been variable
?Heparin	After successful thrombolysis, heparin therapy may reduce the incidence of reocclusion
?Calcium blockers	In several experimental studies in reperfusion models, calcium blockers reduced myocardial infarct size; in clinical studies without reperfusion, they did not affect infarct size; clinical data on combining calcium blockers and reperfusion are limited; calcium blockers do decrease the severity of postinfarct angina and may reduce the incidence of reinfarction in non-Q-wave infarcts
Antiarrhythmics	These may be used for reperfusion arrhythmias
Oxygen-derived radical scavengers to reduce "reperfusion injury"	Current experimental evidence is divided as to whether these agents are beneficial in myocardial infarct models; a United States clinical trial in patients receiving reperfusion for acute myocardial infarction is under way

ISIS-2 = 2nd International Study of Infarct Survival, TIMI II = Phase II Thrombolysis in Myocardial Infarction [trial]

hypothesis that oxygen radicals generated during reperfusion can irreversibly damage a population of myocytes—"reperfusion injury."[127] This suggests that if oxygen radicals are prevented from forming or are scavenged at reflow, reperfusion injury may be blunted. Considerable controversy surrounds both the concept of reperfusion injury per se and the ability of oxygen-radical scavengers administered during reperfusion to prevent it. Most experimental studies have used canine models of 40 to 120 minutes of coronary artery occlusion followed by reperfusion, with an oxygen-radical scavenger or placebo given at reflow. Some investigators observed a substantial reduction in infarct size in animals treated with free-radical scavengers,[127,128] whereas others noted beneficial effects.[129,130]

Our laboratory also investigated reperfusion injury in anesthetized dogs using an open-chest method.[131] We administered superoxide dismutase and catalase after two hours of coronary artery occlusion and maintained treatment for the initial four hours of reperfusion. Four hours after reflow, we observed no overall reduction in infarct size. A retrospective analysis of these data, however, revealed a small subset of moderately ischemic animals in which acute necrosis was less than in controls given a saline solution. We also observed that treatment with superoxide dismutase and catalase blunted the no-reflow phenomenon; regional myocardial blood flow in the previously ischemic endocardium and midmyocardium was considerably greater in treated animals than in saline controls. Electron microscopy showed that enhanced flow after reperfusion in the enzyme-treated animals was accompanied by the preservation of subendocardial microvasculature. Thus, our data suggest that oxygen-radical scavengers consistently reduced microvascular injury produced by two hours of coronary artery occlusion and four hours of reflow but limited acute myocytic injury in only a small group of dogs. In contrast to results obtained in models of transient (15 minutes) occlusion, superoxide dismutase and catalase had no beneficial effect on the return of cardiac function after prolonged (two hours) ischemia. Thus, oxygen radicals may be important contributors to stunned myocardium induced by brief ischemia but are less important in models of prolonged ischemia followed by reperfusion.

Oxygen-radical scavengers may have another important role. Experimental studies in the surgical literature suggest that oxygen-radical scavengers administered as supplements to standard cardioplegic solutions may enhance tissue preservation.[132] A clinical study is being planned to investigate the effect of oxygen-radical scavengers in patients undergoing cardiopulmonary bypass.

Summary and Conclusions

Although timely reperfusion reduces myocardial infarct size, reperfusion may also have deleterious consequences. For example, contractile function of the previously ischemic tissue can remain depressed or stunned for hours to days following reflow. Oxygen free radicals may play a role in this phenomenon. Various studies have reported that free radical-scavenging agents improve contractile function of myocardium stunned by a brief (15-minute) ischemic episode. Calcium-channel blockers have also been shown to enhance the function of stunned, previously ischemic myocardium, leading to speculation that these two seemingly diverse mechanisms may be interrelated.

Oxygen radicals may also contribute to so-called reperfusion injury, but this hypothesis remains controversial. Administering free radical-scavenging agents during reperfusion does not appear to enhance cardiac function in models of prolonged (two-hour) occlusion followed by reflow, and studies of the effect of these agents on myocardial infarct size have shown mixed results. Oxygen-radical scavengers may protect against the no-reflow problem.

Clinical studies provide evidence that other forms of adjuvant therapy (aspirin, β-blockade) may be beneficial in patients with reperfused infarcts. Ongoing and planned clinical studies are assessing the effects of oxygen-radical scavengers as therapy adjuvant for coronary artery reperfusion following infarction and for cardioplegia in patients undergoing cardiopulmonary bypass procedures.

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Hypoglycemias

F. JOHN SERVICE, MD, PhD, *Rochester, Minnesota*

Low concentrations of blood glucose were recognized as a feature of some diseases in the last century. However, it was not until insulin became available for the treatment of diabetes mellitus in the early 1920s that symptoms similar to those arising from overtreatment with insulin were observed in nondiabetic persons. This observation led to the postulation of a new disease entity called *hyperinsulinism.*[1] Support for the existence of hyperinsulinism was provided from the identification of a malignant pancreatic islet cell tumor in 1927 in a patient who had episodes of severe hypoglycemia.[2] Postmortem extracts of metastatic tissue caused marked hypoglycemia in rabbits. The first cure of hyperinsulinism resulted from the successful removal by Graham of an insulinoma in 1929.[3]

Consequent to the development of radioimmunoassay for insulin, hyperinsulinism was confirmed as the pathophysiologic basis for some but not all cases of hypoglycemia.

Physiology of Glucose Homeostasis

Hypoglycemic disorders arise from abnormalities in the mechanisms involved in glucose homeostasis. Unlike many physiologic functions that proceed at relatively steady rates, glucose homeostasis requires mechanisms to respond to the intermittent provision of exogenous nutrients and intervals of no nutrient supply. Processes for energy storage are activated during food ingestion, and those required to release stored energy operate during periods of food deprivation. The resultant effect on glycemia is that of a semidamped system in which plasma glucose is maintained between approximately 70 mg per dl and 180 mg per dl in healthy active persons through a balance between glucose production and glucose utilization.

Postprandial State

Postprandial plasma glucose concentrations are influenced by the size of a meal, its composition, and the time of day it is eaten.

Insulin is the chief modulator of glucose homeostasis (Table 1). The increased concentrations of glucose and various insulinotropic enteric factors following food ingestion stimulate insulin secretion. Insulin suppresses hepatic glucose production and stimulates glucose utilization. Estimates of the relative contributions of these two processes have varied depending on the techniques used for their measurements. Unlike the hepatic vein catheter technique, which measures only net differences across the splanchnic bed, the dual isotope method can estimate hepatic glucose production. Studies in which this technique was used have shown that ≥90% of ingested glucose reaches the peripheral circulation.[4] However, since hepatic glucose production is reduced by 60% to 70% postprandially, the net addition of glucose to the peripheral circulation is reduced by about 35%.[4] Elevated postprandial insulin concentrations (1) promote glycogen formation through the stimulation of glycogen synthetase and suppression of phosphorylase and (2) decrease the concentrations of gluconeogenic precursors, branched-chain amino acids, free fatty acids, and ketone bodies. Suppression of glucose production and inhibition of glycogenolysis are more sensitive to increases in insulin concentration than are stimulation of glucose utilization and inhibition of gluconeogenesis. Following the ingestion of 100 g of glucose, about 10 g of hepatic glycogen is formed by direct uptake of glucose and 10 to 15 g is formed by gluconeogenesis.

Although glucagon is an important glucoregulatory hormone in the postabsorptive state, its role in nutrient disposition postprandially has not been clearly elucidated.

Pari passu with the diminishing absorption of glucose from the intestinal tract and the predominance of glucose utilization over glucose production late postprandially, the plasma glucose concentration falls. Concomitantly the plasma insulin concentration decreases. The waning effect of insulin restores glucose utilization and production to preprandial rates. At this point there is a transition from a state of glucose storage to one of carefully husbanded glucose production at rates that satisfy the obligatory requirements of the glucose-dependent tissues.

Postabsorptive State

About 4 to 6 hours after food ingestion, plasma glucose concentrations are 80 to 90 mg per dl and rates of glucose utilization and production are approximately 2 mg per kg per min. Glucose production is primarily (70% to 80%) from hepatic glycogenolysis, with a lesser contribution (20% to 25%) from hepatic gluconeogenesis.[5] After an overnight fast, the liver contains 40 to 50 g of glucose in the form of glycogen. On the assumption that there is an obligatory rate of glucose utilization of 1 to 1.5 mg per kg per min, glycogen stores should be depleted after 24 to 36 hours of fasting. In the postabsorptive state glucagon stimulates glucose production by enhancing glycogenolysis and gluconeogenesis and by inhibiting glycolysis (Table 1). Glucagon activates glycogen phosphorylase and inactivates glycogen synthetase. Glucagon has no known direct effect on extrahepatic glucose uptake. Basal concentrations of catecholamines do not appear to influence glucose homeostasis in the postabsorptive

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From the Department of Internal Medicine, Division of Endocrinology, Mayo Clinic. Dr Service is Professor of Medicine, Mayo Medical School, Rochester, Minnesota.

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Reprint requests to F. John Service, MD, PhD, Department of Internal Medicine, Division of Endocrinology, Mayo Clinic, Rochester, MN 55905.

state. Cortisol seems to have a permissive effect on glucose metabolism. Its presence is needed for normal glycogen synthesis and for the acceleration of glucose production by glucagon and epinephrine (Table 1). Cortisol antagonizes the actions of insulin and thereby accelerates gluconeogenesis, lipolysis, ketogenesis, and proteolysis and decreases glucose utilization. The hyperglycemic effect of cortisol is not immediate but delayed by two hours. Cortisol decreases both hepatic and extrahepatic sensitivity to insulin.[6]

Glycogenolysis

Glycogen, a polymer of glucose, serves as a reservoir for glucose. Although glycogen is stored in both the liver and skeletal muscle, only the liver and kidney possess the enzymes capable of yielding free glucose. In muscle, glycogen breakdown yields lactate, which, after transport to the liver, may enter the gluconeogenic pathway (Figure 1). Glycogenolysis involves the activity of several enzymes. Phosphorylase, which is stimulated by glucagon and epinephrine but inhibited by insulin, cleaves glycogen, to liberate glucose-1-phosphate, at alpha 1 to 4 linkages up to within 3 to 5 glycosyl units of a 1,6 branch point. After oligo 1,4–1,6-glycan transferase (a debrancher), which splits the 1,6 linkages, has acted, phosphorylase activity can continue. Amylo-1,6-glucosidase releases free glucose. Phosphoglucomutase converts glucose-1-phosphate to glucose-6-phosphate, which can be hydrolyzed to free glucose by glucose-6-phosphatase. Since the latter enzyme is present only in the liver and kidney, only these organs can provide free glucose. Deficiency of glucose-6-phosphatase results in severe hypoglycemia; deficiencies of phosphorylase and debrancher enzymes cause mild degrees of hypoglycemia.[7]

Approximately half of the glucose utilized (1 mg per kg per min) is committed to the obligatory noninsulin-mediated uptake of glucose by the brain.[8] As plasma glucose in patients with insulinomas reached concentrations at the threshold level for the occurrence of symptoms of hypoglycemia, glucose utilization rates were 1.3 mg per kg per min.[9]

In the postabsorptive state the daily glucose consumption by a person weighing 70 kg is approximately 30 g by muscle, 120 g by brain, 34 g by blood elements, and 2 g by the renal medulla.

Fasting State

After several days of food deprivation, plasma glucose concentrations fall to 45 to 60 mg per dl; these levels can be maintained for several weeks. Rates of glucose utilization

TABLE 1.—*Hormonal Control of Glucose Homeostasis*

Hormone	*Hepatic Glucose Production*	*Extrahepatic Glucose Utilization*	*Basal Glucose Production*	*Relative Importance to Recovery From Insulin-Induced Hypoglycemia*
Insulin	↓	↑	↓	...
Glucagon	↑	–	↑	+++
Catecholamines*	↑	↓	–	+
Cortisol	↑	↓	↑	–
Growth hormone†	↑	↓	–	–

↑ = increase, ↓ = decrease, – = no effect

*Epinephrine is approximately 10 times more potent than norepinephrine. Its action is primarily through a β-adrenergic mechanism. In the presence of glucagon deficiency, catecholamines make a modest contribution to the recovery from hypoglycemia.

†Have an acute and transient hypoglycemic effect.

From Service FJ: Hypoglycemic disorders. In Wyngaarden JB, Smith LH (Eds): Cecil Textbook of Medicine, 18th Ed. Philadelphia, W8 Saunders Company, 1988, pp 1381-1387.

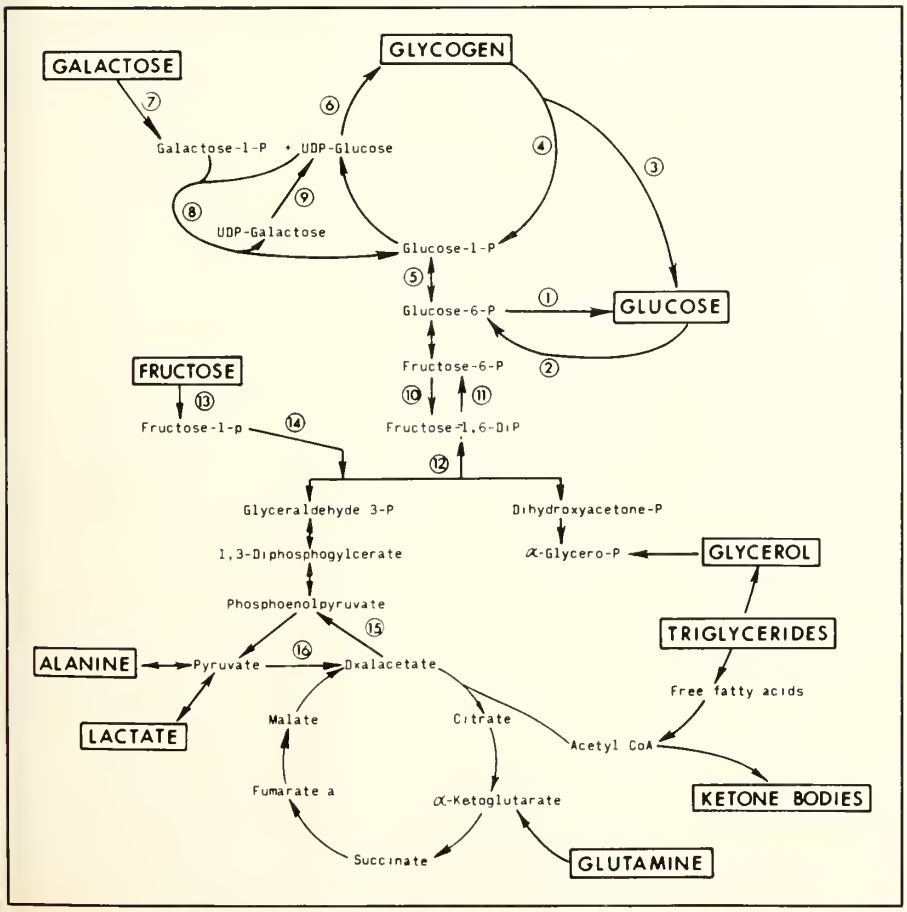

Figure 1.—Metabolic pathways involved in glycogen synthesis and degradation and gluconeogenesis. Key enzymes are designated by number. (1) glucose 6-phosphatase, (2) glucokinase, (3) amylo-1,6-glucosidase, (4) phosphorylase, (5) phosphoglucomutase, (6) glycogen synthetase, (7) galactokinase, (8) galactose 1-phosphate uridyl transferase, (9) uridine diphosphogalactose-4-epimerase, (10) phosphofructokinase, (11) fructose 1,6-diphosphatase, (12) fructose 1,6-diphosphate aldolase, (13) fructokinase, (14) fructose 1-phosphate aldolase, (15) phosphoenolpyruvate carboxykinase, (16) pyruvate carboxylase. (Modified from Pagliara AS, et al: Hypoglycemia in infancy and childhood. Part I. J Pediatr 1973; 82:365, with permission.)

decrease to approximately 1 mg per kg per min and remain constant thereafter. During this period, plasma free fatty acid and ketone body concentrations increase; these substances serve as energy sources for muscle. Furthermore, ketone bodies replace glucose as the predominant fuel for neural tissues, thereby reducing the obligatory glucose uptake by the brain.[10] Women tolerate food deprivation less well than do men.

Gluconeogenesis

Gluconeogenesis is the process by which new glucose is synthesized from noncarbohydrate precursors. Since this process sustains glucose production after glycogen depletion, hypoglycemia arising from defective gluconeogenesis should be evident only after prolonged food deprivation. Lactate, pyruvate, glycerol, and amino acids are the major gluconeogenic substrates. Because not all glycolytic enzymes have reversible activity, another series of enzymes—pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-diphosphatase, and glucose-6-phosphatase—is required to effect the conversion of gluconeogenic substrates to free glucose (Figure 1). The relative contributions to gluconeogenesis of various substrates are: lactate and pyruvate 60%, glycerol 13%, and amino acids 29%.[5] Substrate availability can be an important modulator of gluconeogenesis, since the concentrations of these precursors in the postabsorptive state are below those necessary for maximal rates of gluconeogenesis. Lactate is derived primarily from erythrocytes, skeletal muscle, brain, and skin. Adipose tissue is the source of glycerol. Skeletal muscle is the chief source of alanine and glutamine, the most important amino acid substrates for gluconeogenesis. Alanine is derived largely from the transamination of pyruvate from branched-chain amino acids (leucine, isoleucine, and valine), which act as nitrogen donors. Branched-chain amino acids may account for as much as 60% of alanine nitrogen. The importance of amino acids for glucose homeostasis during fasting is illustrated by the occurrence of hypoglycemia when alanine availability is reduced because of the impairment of leucine metabolism in maple syrup urine disease.[11]

Gluconeogenesis from alanine is increased by 100% after 48 hours of fasting. With more prolonged food deprivation the contribution of alanine to gluconeogenesis decreases. In contrast, plasma lactate concentration does not wane during prolonged starvation, and its contribution to gluconeogenesis remains constant at 50% above postabsorptive levels. After 30 hours of fasting, differences among men, women, and children have been observed in gluconeogenic substrates. Children had the lowest plasma glucose and alanine and highest beta-hydroxybutyrate concentrations, with those in men being the obverse and those in women being intermediate. After 86 hours of fasting, leucine, valine, and isoleucine concentrations increase, whereas levels of aspartate, threonine, serine, proline, glycine, alanine, methionine, tyrosine, phenylalanine, and glutamine remain essentially unchanged.[12]

Even in the presence of adequate gluconeogenic precursors, gluconeogenesis may be inhibited by an alteration in the cellular redox state, the effect of which is to inhibit gluconeogenic enzymes—e.g., alcohol hypoglycemia. The metabolism of ethanol results in an increase in $NADH/NAD^+$ ratio with an attendant decrease in the conversion of lactate, alanine, and glycerol to glucose. Hypoglycemia may occur following ingestion of the unripe ackee fruit through the interference with gluconeogenesis by the inhibition of pyruvate carboxylase and fatty acid oxidation.[13]

Mechanisms of Recovery From Hypoglycemia

Coincident with the recovery phase of acute hypoglycemia are marked increases in concentrations of plasma, glucagon, and epinephrine (Table 1). Increases in plasma concentrations of cortisol and growth hormone occur later. When permissive amounts of cortisol and growth hormone are present, further increases in their concentrations are not necessary for recovery from hypoglycemia. Acute increases in plasma concentrations of growth hormone decrease plasma glucose whereas more prolonged increases cause hyperglycemia. The latter effect is mediated by decreasing glucose utilization and stimulating glucose production through an action antagonistic to insulin. In contrast, glucagon is essential for normal recovery from hypoglycemia.[14] Catecholamines do not appear to be essential for recovery from hypoglycemia as long as glucagon secretion is intact.[14] However, catecholamines are necessary for recovery from hypoglycemia in the presence of glucagon deficiency[14] or when hypoglycemia is profound (Figure 2).

Catecholamines increase glucose production directly by stimulating both glycogenolysis and gluconeogenesis and indirectly by stimulating glucagon release (Table 1). Epinephrine also decreases glucose utilization by directly inhibiting tissue glucose uptake and by inhibiting insulin release. Epinephrine is approximately 10 times more potent than norepinephrine in producing these effects. Epinephrine stimulates glucose production directly by a beta-adrenergic mechanism and indirectly by inhibiting insulin secretion by an alpha-adrenergic mechanism. Glucose counterregulation from insulin-induced hypoglycemia is primarily by glycogenolysis during the first two hours and then from gluconeogenesis thereafter (Figure 3).[15]

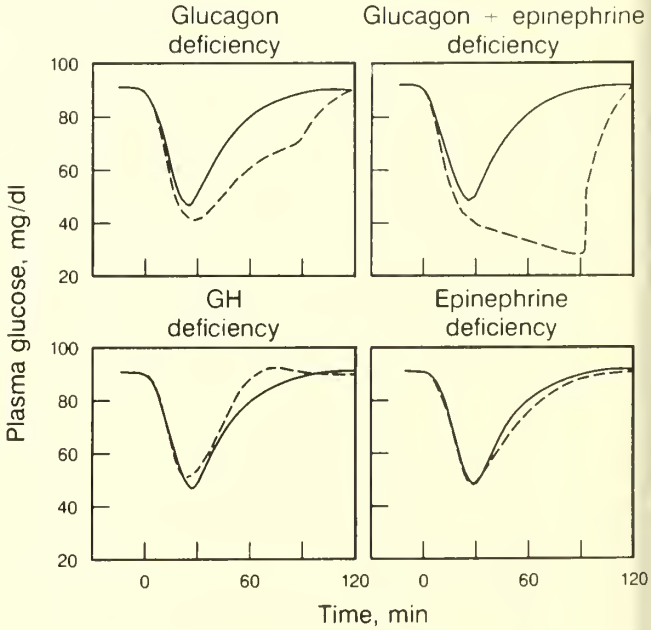

Figure 2.—Plasma glucose curves during insulin-induced hypoglycemia in man with counterregulation intact (solid lines) and during selective blockade of counterregulatory hormones (dashed lines). (Modified from Cryer, et al: Roles of glucagon and epinephrine in hypoglycemic and nonhypoglycemic glucose counterregulation in humans. Am J Physiol 1984; 247 [Endocrinol Metab 10]:E198, with permission.)

Classification of Hypoglycemic Disorders

Hypoglycemic disorders may be classified in several different ways. A classification may separate disorders on the basis of a biochemical characteristic, e.g., hyperinsulinemia, or on the basis of pathophysiologic behavior, e.g., rates of glucose production and utilization. Categorization of hypoglycemic disorders by insulin concentration is less than ideal because some disorders mediated by insulin-like action are not associated with hyperinsulinemia. In addition, hypoglycemic disorders do not segregate easily by rates of glucose turnover, viz., those due to overutilization of glucose and those due to underproduction of glucose. Hypoglycemia cannot be generated unless the rate of glucose utilization exceeds that of glucose production. Insulinoma, the condition anticipated to be the quintessential model of excessive glucose utilization, has been found to be associated with lower than normal rates of glucose utilization and production[9] (Figure 4). To date, a hypoglycemic disorder entirely due to excessive glucose utilization in the face of normal glucose production has not been confirmed by isotopic assessments of rates of glucose turnover. However, large amounts of glucose have been required to control hypoglycemia in patients with nonislet cell tumor[16] and in patients with malnutrition.[17] Considering the paucity of data on glucose flux rates in hypoglycemic states, classification by this criterion seems unwarranted. Since patients primarily manifest clinical features, an expeditious classification may be one related to clinical presentation (Figure 5).

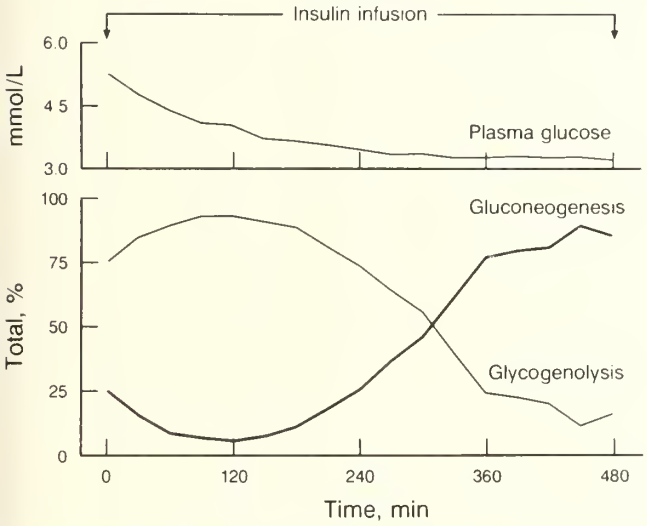

Figure 3.—Time course of contributions of gluconeogenesis and glycogenolysis to overall hepatic glucose output during glucose counterregulation against insulin-induced hypoglycemia in healthy subjects. (Modified from Lecavalier L, et al: Contributions of gluconeogenesis and glycogenolysis during glucose counterregulation in normal humans. Am J Physiol 1989; 256 [Endocrinol Metab 19]:E844.)

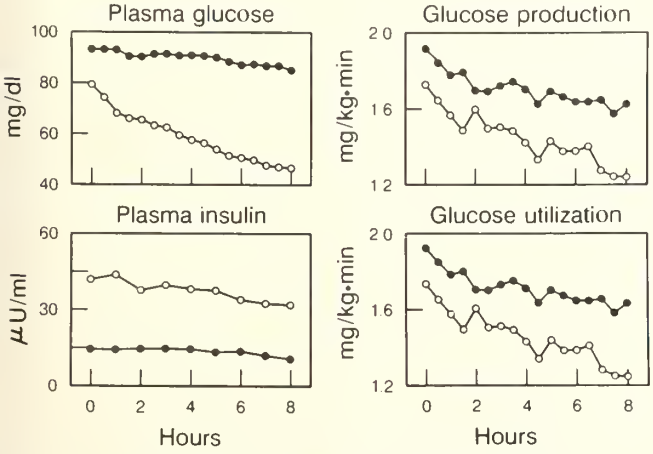

Figure 4.—Plasma glucose and insulin levels and rates of glucose production and utilization in 6 insulinoma patients and 8 normal subjects during an 8-hour fast. (Modified from Rizza RA, et al: Pathogenesis of hypoglycemia in insulinoma patients. Diabetes 1981; 30:377, with permission.)

Clinical Evaluation

Defects of many of the mechanisms that maintain plasma glucose in the normal range are associated with readily recognizable clinical syndromes. In some instances the symptoms and signs of the primary disorder predominate over those of hypoglycemia or at least point to the existence of the primary disorder. In some patients with such conditions as multisystem disease, poor nutrition, and multiple drug use, the basis for hypoglycemia may be uncertain and the patient too ill to undergo extensive evaluation.

In the majority of patients with symptoms of hypoglycemia who appear healthy, screening laboratory tests should include plasma glucose, insulin, calcium, phosphate, uric acid, lipids, creatinine, insulin antibodies, cortisol, and liver function. Documentation of drug-induced hypoglycemia may be difficult. A detailed history must be obtained, and every medication, including nonprescription drugs, used by the patient must be examined.

When a patient is observed with symptoms of hypoglycemia, 10 to 20 ml of blood in addition to that for glucose determination should be withdrawn. The specific analyses to be done on the saved specimen can be determined by clues generated from the history and physical examination. Such an opportunity may provide sufficient data to establish the cause of the hypoglycemic disorder or at least narrow the diagnostic possibilities. Glucose or glucagon should be administered following blood withdrawal to any patient suspected of being hypoglycemic. Prompt treatment will shorten the duration of hypoglycemia, and, if the patient is not hypoglycemic, no harm will be done.

In patients with asymptomatic hypoglycemia one must be alert for artifactual hypoglycemia. Whole blood glucose values may be spuriously low in polycythemia vera because of the unequal distribution of glucose between erythrocytes and plasma or excessive glycolysis by erythrocytes, or both. Low blood glucose values in leukemia are due to excessive glycolysis by leukocytes and in hemolytic crisis from excessive glycolysis by nucleated erythrocytes. In the polycythemic patient or in serum of the leukemic or hemolytic patient, prompt measurement of glucose in plasma to which an antiglycolytic agent has been added should provide accurate results.

An uncommon and challenging problem is the low plasma glucose concentration in an asymptomatic patient in whom laboratory error and spurious result have been ruled out. Such patients may have adapted to long-standing hypoglycemia or have mild symptoms that have been unrecognized.

A flow diagram of a clinical approach to the evaluation of a suspected hypoglycemic disorder is presented in Figure 5. Note that the evaluation is directed to patients who appear healthy. For those who do not appear healthy the results of the

history and physical examination will determine the direction of the investigation.

Hypoglycemic disorders cause a constellation of symptoms that usually recur as discrete episodes at irregular intervals. A useful but not infallible historical aid is the timing of symptoms in relation to food intake: those occurring within four hours of food intake are due to the food-stimulated hypoglycemias and those occurring beyond five hours of food intake are due to the food-deprived hypoglycemias.

Considerable effort should be expended to obtain from the patient and family members a detailed description of symptoms and careful attention paid to their occurrence in relation to food intake (Figure 6). Symptoms may result from activation of the autonomic nervous system (sweating, shakiness, anxiety, palpitations, and weakness) or impairment of central nervous system function (reduced intellectual capacity, confusion, irritability, abnormal behavior, convulsions, and coma). Hypothermia may be an accompaniment. Sometimes the autonomic symptoms that precede the central nervous system symptoms go unrecognized. Symptoms of hypoglycemia usually occur at plasma glucose concentrations of about 45 mg per dl or less (whole blood glucose of 40 mg per dl or less).[18] Although some studies suggest that a rapid fall in glucose concentration results in symptoms even when plasma glucose does not decrease below 45 mg per dl, the weight of evidence does not support this relationship.[19]

The symptoms of hypoglycemia are nonspecific. For this reason it is necessary to demonstrate a low plasma glucose value concomitant with symptoms and subsequent relief of symptoms by correction of the hypoglycemia, i.e., *Whipple's triad.*[20] This triad should be demonstrated before hypoglycemia can be considered to be the basis for a patient's symptoms. Although food—especially free carbohydrate—will relieve symptoms regardless of the cause of the hypoglycemia, persons without a hypoglycemic disorder may feel better after eating. It is, therefore, imperative to confirm that symptoms are due to biochemically confirmed low glucose concentration. The tests available for evaluation of patients with a hypoglycemic disorder are meal test, intravenous tolbutamide test, C-peptide suppression test, and intravenous glucagon test (postabsorptive and/or when hypoglycemic) and prolonged supervised fast. For those food-deprived hypoglycemias associated with elevated plasma insulin levels, measurement of plasma C-peptide permits a determination to ascertain whether the hyperinsulinemia is endogenous or exogenous in origin (Figure 7).

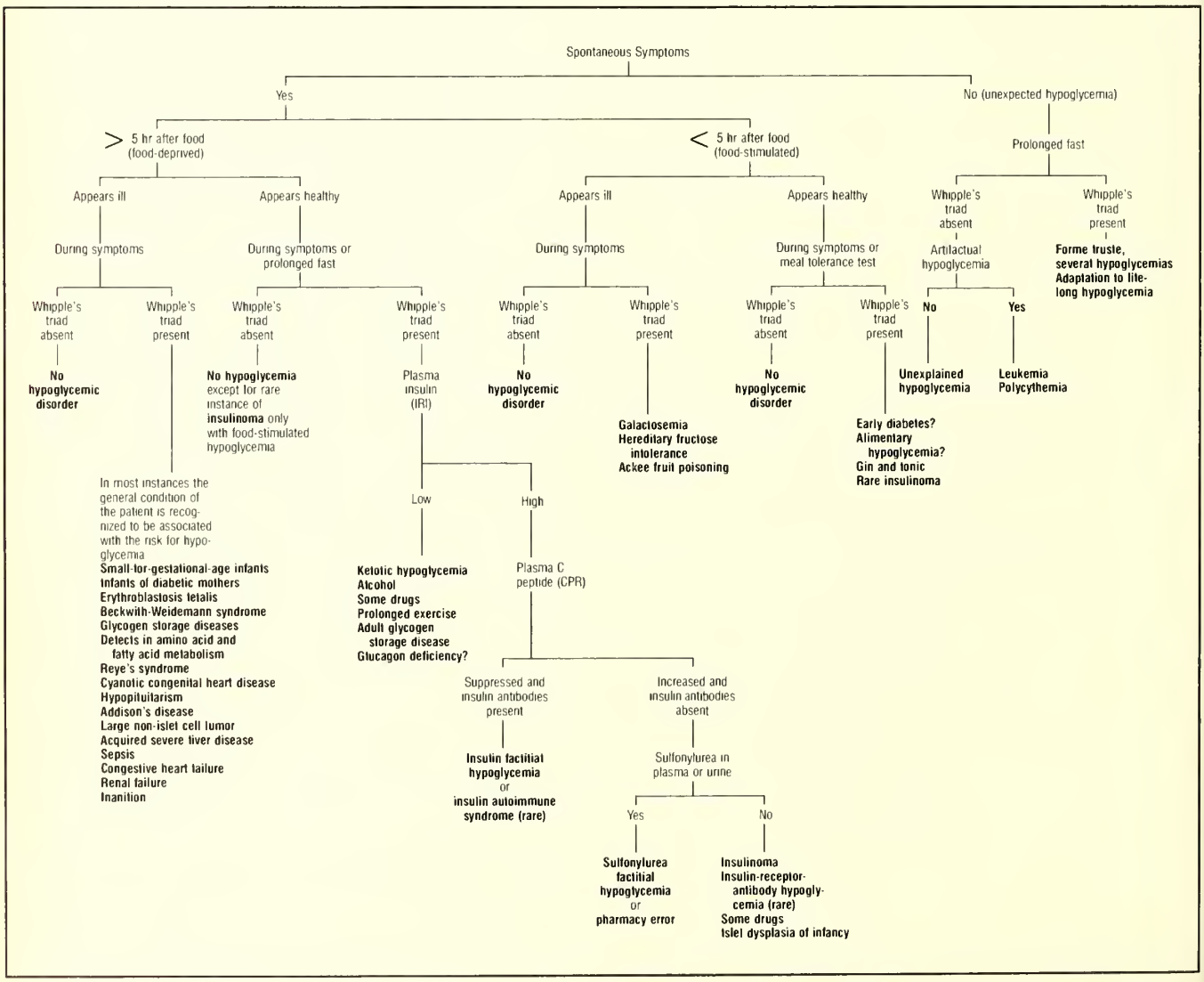

Figure 5.—Evaluation of hypoglycemic disorders. (Modified from Service FJ: Hypoglycemic disorders, *In* Wyngaarden JB, Smith LH Jr (Eds): Cecil Textbook of Medicine, 18th Ed. Philadelphia, WB Saunders Company, 1988, pp 1381-1387.)

Food-stimulated Hypoglycemias

Subsequent to the conceptualization of hyperinsulinism, many patients with postprandial symptoms of the autonomic type were found to have normal concomitant blood sugar concentrations. For such cases the term functional hyperinsulinism was coined.[21] Eventually, reliance on a subnormal glucose concentration at the time of spontaneous symptoms came to be replaced by the oral glucose tolerance test.[22] Reproduction of postprandial symptoms experienced in daily activities during the oral glucose tolerance test associated with a plasma glucose nadir ≤50 mg per dl (or its equivalent) has been considered confirmation of the presence of a food-stimulated hypoglycemic disorder.[23] Use of the oral glucose tolerance test is fraught with risk of misdiagnosis, since (1) at least 10% of healthy persons have plasma glucose nadirs <50 mg per dl;[23,24] (2) there is no correlation between the nadir of plasma glucose concentrations and the occurrence of autonomic symptoms;[25] and (3) the results of oral glucose tolerance tests are variable upon repeated testing.[26] Plasma cortisol responses, rates of glucose descent, hypoglycemic indices, and plasma epinephrine responses—all of which have been recommended to improve the accuracy of the oral glucose tolerance test—have failed to do so or have not been assessed during placebo oral glucose tolerance tests. In fact, many patients with postprandial autonomic symptoms experience symptoms after a "placebo" oral glucose tolerance test.[24]

Patients with postprandial autonomic symptoms generally have been classifiable into one of three categories: those with normal oral glucose tolerance tests (functional hypoglycemia); those who have undergone surgical modification of the upper gastrointestinal tract (alimentary hypoglycemia), and those with elevated one- and two-hour glucose levels in an oral glucose tolerance test (early diabetes hypoglycemia). The incidence of hypoglycemia postprandially in patients after gastric surgery varies from 5% to 37%. Alimentary hypoglycemia has been reported in patients who have undergone a variety of surgical procedures (gastrectomy, gastroenterostomy, vagotomy, and pyloroplasty) and in some with intact GI tracts and is characterized by symptoms of hypoglycemia two hours postprandially. This phenomenon should be distinguished from the dumping syndrome, which may cause similar symptoms but occurs within an hour of eating, is unassociated with hypoglycemia, and is presumed to be caused by contraction of the plasma volume due to fluid shift into the gastrointestinal tract. Although plasma glucose nadirs ≤50 mg per dl during oral glucose tolerance testing in patients who have undergone these surgical procedures are not uncommon, hypoglycemic symptoms are much less frequently seen.[27]

Of 101 patients considered to have early diabetes with a blood glucose of <50 mg per dl at the fourth or fifth hour after an oral glucose load, <5% had had symptoms of hypoglycemia after meals.[28] No correlation has been found between the presence of symptoms of hypoglycemia postprandially during ordinary life and the severity of the hypoglycemia during the oral glucose tolerance test, regardless of subtype.

Unfortunately, the basis for the postprandial symptoms is

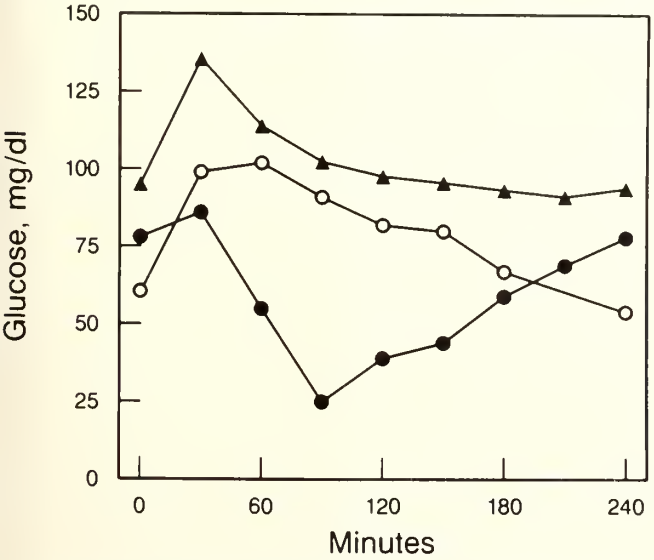

Figure 6.—Differential plasma glucose responses to a mixed meal between food-stimulated hypoglycemia (closed circle) and food-deprived hypoglycemia (open circle) in contrast to healthy subjects (triangle).

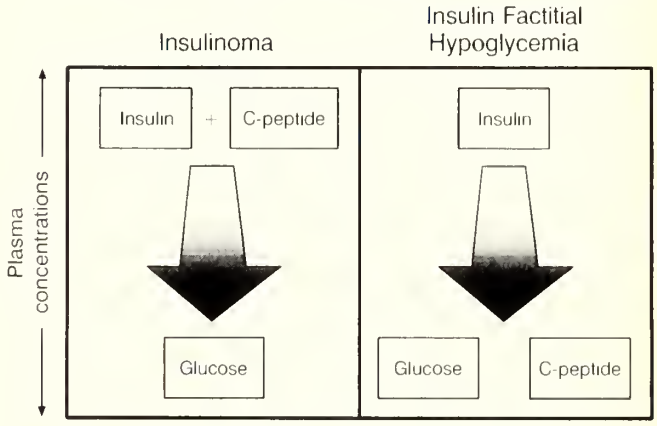

Figure 7.—Endogenous hyperinsulinemia from insulinoma is associated with elevated C-peptide concentrations with concurrent hypoglycemia. Exogenous hyperinsulinemia from injected insulin results in low concentrations of C-peptide both because of the effect of the associated hypoglycemia and because of the direct suppressive effect of insulin on the pancreatic beta cell. (Modified from Service FJ: Hypoglycemic disorders, *In* Wyngaarten JB, Smith LH Jr (Eds): Cecil Textbook of Medicine, 18th Ed. Philadelphia, WB Saunders Company, 1988, pp 1381-1387.)

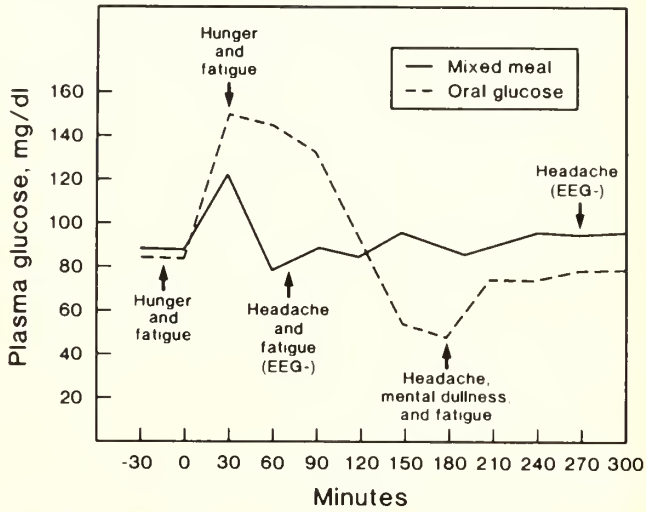

Figure 8.—Plasma glucose responses to oral glucose tolerance test contrasted to responses to a mixed meal in patients with postprandial symptoms suggestive of food-stimulated hypoglycemia. Despite symptoms during both tests, no EEG abnormalities were found.

obscure in patients in most published reports because glucose concentrations usually were never measured during spontaneous symptoms. In one study in which patients collected capillary blood on filter paper at the time when postprandial symptoms were present, centrally measured blood glucose levels were almost invariably not in the hypoglycemic range.[29]

When plasma glucose responses to a mixed meal were compared with those following an oral glucose tolerance test, none of the patients who had a hypoglycemic nadir after oral glucose evinced hypoglycemia after the mixed meal or any EEG evidence of hypoglycemia[30] despite the occurrence of symptoms during both tests (Figure 8). Therefore, the oral glucose tolerance test should not be used for the evaluation of hypoglycemia in patients with symptoms in the postprandial period. Instead, plasma glucose should be measured during the spontaneous occurrence of symptoms or after ingestion of a meal typical of that followed by symptoms.[29]

Unfortunately, reliance on the oral glucose tolerance test for the diagnosis of food-stimulated hypoglycemia has led to extensive publications not on disorders of hypoglycemia but on the oral glucose tolerance test. Most persons with autonomic symptoms following meals have been shown to have psychoneurosis.[25] The use of low-carbohydrate/high-protein or high-fiber diets, sulfonylureas, biguanides, and anticholinergic agents for the treatment of food-stimulated hypoglycemias has only limited scientific support. Hypoglycemia following the ingestion of substances that are toxic to susceptible persons may be considered in the category of food-stimulated hypoglycemias, e.g., in children with galactosemia and hereditary fructose intolerance.

The ingestion of large amounts (equivalent to three highballs) of ethanol and simple carbohydrate (gin and tonic) but not complex carbohydrate may cause hypoglycemia within three to four hours in some healthy persons.

The unripe ackee fruit may result in hypoglycemia in children and adults with chronic malnutrition.[13]

Food-deprived Hypoglycemias

Drug-induced Hypoglycemias

Drugs constitute the most common cause of hypoglycemia when insulin and sulfonylurea treatments of diabetic persons are included.[31] Factors that increase the risk for drug-induced hypoglycemia are extremes of age, antecedent food deprivation, and impaired renal and hepatic function. Salicylates may cause hypoglycemia in children.[31] Propranolol has been implicated as a contributor to hypoglycemia in patients with other potentially hypoglycemia-provoking conditions.[31] Other drugs recently reported to cause hypoglycemia are disopyramide (Norpace), sulfamethoxazole and trimethoprim (Bactrim, Septra) in the presence of renal failure, pentamidine (Lomidine), and quinine when used for cerebral malaria. Since a wide variety of drugs has been implicated as the cause of hypoglycemia, the reader is referred to review articles on this subject.[31] Ethanol-induced hypoglycemia arises from inhibition of gluconeogenesis as a result of the increase in the $NADH/NAD^+$ ratio in instances of depleted hepatic glycogen.[32] The increased $NADH/NAD^+$ ratio suppresses the conversions of lactate to pyruvate, alpha-glycerophosphate to dihydroxyacetone phosphate, and glutamate to alpha-ketoglutarate and several tricarboxylic cycle reactions. Infusion of ethanol into healthy subjects for four hours was observed to result in hypoglycemia; reduced rates of hepatic glucose production; suppressed plasma insulin concentrations; increased plasma lactate, beta-hydroxybutyrate, glycerol, and free fatty acid concentrations; and increased lactate/pyruvate and beta-hydroxybutyrate/acetoacetate ratios.[33] Hypoglycemia usually develops within 6 to 36 hours of the ingestion of even moderate amounts of ethanol by persons chronically malnourished or by healthy persons who have missed one or two meals. Children, even though healthy, are especially susceptible to ethanol-induced hypoglycemia. Blood alcohol levels may not be elevated when the patient is hypoglycemic.

Hypoglycemia Due to Insulinoma

Approximately 60% of patients with insulinoma are female.[34] Insulinomas are uncommon in persons younger than 20 years of age and rare in those younger than 5 years. The median age at diagnosis is about 50, except in patients with the multiple endocrine neoplasia (MEN) syndrome, in which it is in the mid-20s.[34] Ten percent of patients with insulinoma are older than 70 years of age.[34]

Of patients with insulinoma, 80% have single benign tumors, 11% have multiple benign tumors, 6% have single malignant tumors, and the remainder have multiple malignant tumors or islet hyperplasia.[34] Ten percent of insulinoma patients have MEN syndrome type I, and 80% of these patients have multiple insulinomas. The commonest associated endocrine abnormality is primary hyperparathyroidism; pituitary tumors appear in approximately 50% of the patients.[34] Only 60% of patients with multiple insulinomas have the MEN syndrome.[34]

Some tumors secrete hormones in addition to insulin: gastrin, 5-hydroxyindoles, ACTH, glucagon, and somatostatin. In rare instances, insulinomas have occurred in non-insulin-dependent diabetic persons[35] but have never been documented in an insulin-dependent subject. Insulinomas have been successfully removed from pregnant women.[34]

Clinical Picture. Symptoms may be present for as short a time as one week and as long as many years before the diagnosis. The longest duration of confirmed hypoglycemic episodes has been 23 years.[36] In a series of 95 patients with insulinomas, 85% of patients had various combinations of

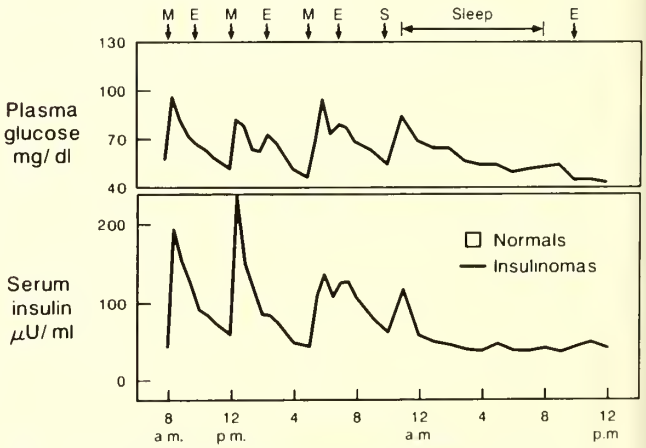

Figure 9.—Serial measurements of plasma glucose and serum insulin in patients with insulinoma and healthy subjects under ordinary life conditions. Plasma glucose declined to hypoglycemic levels in the late postabsorptive and fasting states in those with insulinoma. Hyperinsulinemia was observed in response to meals and also in the postabsorptive and fasting states. (M = meal; S = snack; E = exercise) (Modified from Service FJ and Nelson RL: Insulinoma. Compr Ther 1980; 2:70, with permission.)

diplopia, blurred vision, sweating, palpitations, and weakness; 80% had confusion or abnormal behavior; 53% had unconsciousness or amnesia; and 12% had grand mal seizures.[34] Twenty percent of cases may be misdiagnosed, the belief being that the patient has a neurologic or psychiatric disorder.[34]

Hypoglycemia usually occurs several hours after a meal, most commonly before the evening meal[18] (Figure 9). In rare instances, symptoms may occur solely in the postprandial period rather than during fasting.[34] Symptoms may be aggravated by exercise, alcohol use, a high protein–low carbohydrate diet, treatment with sulfonylureas, and religious fasts.[34] Less than 20% of patients with insulinoma gain weight.[18] Hypoglycemic peripheral neuropathy has been observed in rare cases of insulinoma.[37]

Diagnosis. The diagnosis of insulinoma is based on the demonstration of Whipple's triad and hyperinsulinemia (or an inappropriately "normal" insulin level for a low glucose value). Although insulin antibodies are usually undetectable,[34] in rare instances minimal titers of insulin antibodies in patients with surgically proved insulinoma have been noted. Useful outpatient diagnostic tests are the intravenous tolbutamide (IVTT) and C-peptide suppression tests. These tests should not be performed unless the fasting plasma glucose is known to exceed 50 mg per dl before the test. (Concern about the safety of the IVTT is based on two reports of serious side effects. However, in those reports tolbutamide was injected when patients were already significantly hypoglycemic.) When it is verified that the preinjection plasma glucose is ≥50 mg per dl, no adverse effects have been observed.[38] The IVTT should not be performed in anyone who has been food-deprived for several days (e.g., immediately after a 72-hour fast), in anyone with poor nutrition, or in patients with severe liver disease. Neither test should be conducted in a patient with hypopituitarism or hypoadrenocorticism who has not taken the morning dose of replacement glucocorticoid.[34]

The criterion that provides the best accuracy for diagnosis is to average the plasma glucose values at 120, 150, and 180 minutes after tolbutamide administration (Figure 10). If the mean value at these time points is less than 55 mg per dl for lean persons and 62 mg per dl for obese persons there is a high likelihood (>95 sensitivity with 95% specificity) that the patient has an insulinoma. There is less accuracy for diagnosis by using the ratio of the plasma glucose at 180 minutes after tolbutamide to the fasting value or by examination of the plasma insulin responses. If the plasma glucose responses to intravenous tolbutamide are normal, the insulin values should be ignored.[34,38] The C-peptide suppression test is based on the observation that hypoglycemia induced by exogenous insulin fails to suppress C-peptide concentration normally in those with insulinomas[39] (Figure 11). The criteria for normal C-peptide suppression will depend on the C-peptide assay. The euglycemic C-peptide suppression test involves maintenance of euglycemia during insulin infusion. This approach relies on inhibition of insulin release by insulin and has the advantage of avoiding hypoglycemia. It is difficult to know how useful this approach to C-peptide suppression is; it has been used in only a few patients. Furthermore, if the patient is hypoglycemic before the test, the test is virtually in progress: measurement of plasma glucose, insulin, and C-peptide will provide a diagnosis. If the patient is not hypoglycemic, the standard test (insulin infusion without glucose clamping) can be conducted. Plasma glucose responses to intravenous glucagon, whether at the end of a prolonged fast or in the postabsorptive state, provide useful diagnostic information. Blunted plasma glucose response suggests glycogen storage disease or another hepatic disorder that precludes glycogenesis or glycogenolysis. Blunted plasma glucose response at the end of a prolonged fast but normal response in the postabsorptive state indicates intact glycogenolysis and suggests impaired substrate availability.

If repeated demonstration of Whipple's triad and hyperinsulinemia during routine activities is not feasible, the patient should undergo a supervised fast. During the fast the patient should be active during the day and may consume noncaloric beverages. The frequency of blood sampling is influenced by the patient's history of tolerance to food withdrawal (e.g., every six hours) and may be increased (e.g., every one to two hours) as the plasma glucose approaches the hypoglycemic range. Whenever blood is taken for glucose determination,

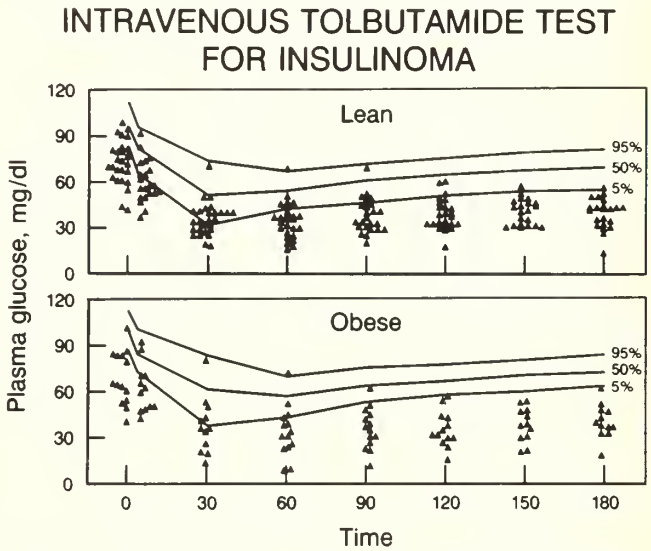

Figure 10.—The 5th, 50th, and 95th percentile plasma glucose responses to intravenous tolbutamide test are shown for lean and obese control subjects in contrast to responses (triangles) in lean and obese patients with histologically confirmed insulinoma. (Modified from McMahon MM, et al: Mayo Clin Proc 1989; 64:1481.)

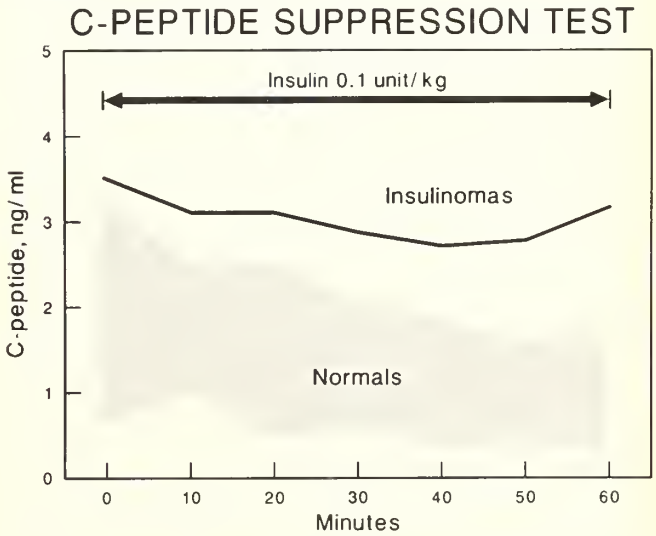

Figure 11.—C-peptide suppression test in insulinomas (M ± SEM) and controls (shaded). In response to insulin-induced hypoglycemia, insulinomas fail to suppress C-peptide. (Modified from Service FJ and Nelson RL: Insulinoma. Compr Ther 1980; 2:70.)

plasma insulin and C-peptide should also be measured. Plasma should be submitted for sulfonylurea measurement if surreptitious ingestion of this drug is suspected. The patient's intellectual status should be checked regularly by simple mathematic tasks such as serial 7s. During prolonged fasting, healthy women may experience lower plasma glucose concentrations than those noted in healthy men: values as low as the low 40s in men and mid-30s in women may be unaccompanied by symptoms.[34] Therefore, it is essential to continue the fast to the point at which symptoms develop, or to 72 hours. Upon demonstration of Whipple's triad, the fast may be terminated by the intravenous injection of glucagon, 1 mg. An increase in plasma glucose (>15 mg per dl) within 30 minutes is observed in patients whose hypoglycemia is mediated by insulin or an insulin-like factor. A blunted response is consistent with a non–insulin-mediated hypoglycemic disorder (Figure 12). Plasma insulin concentrations may be in the "normal" range in about 50% of determinations when the plasma glucose is in the hypoglycemic range; 10% to 20% of patients with insulinoma may have all insulin values in the "normal" range during hypoglycemia; however, the plasma insulin concentration is probably excessive if it is above 6 μU per ml and certainly excessive if it is above 10 μU per ml during hypoglycemia (Figure 13). Various glucose-insulin ratios provide less diagnostic accuracy.[34]

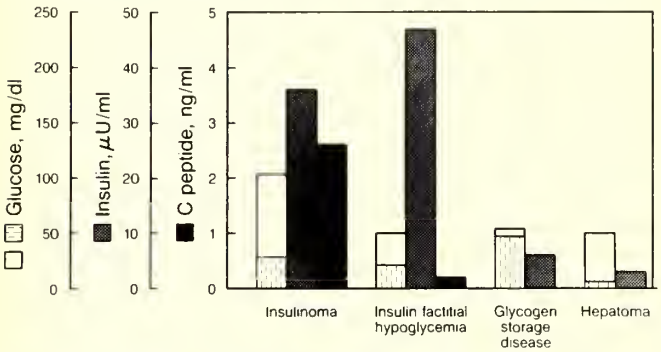

Figure 12.—Plasma glucose, insulin, and C-peptide response to intravenous injection of glucagon in the fasting state in four different types of food-deprived hypoglycemia. Insulinoma is characterized by high insulin and C-peptide levels, whereas insulin factitial hypoglycemia has high insulin but suppressed C-peptide levels; both respond normally to glucagon injection (white bar above basal glucose, hatched bar). Glycogen storage disease shows suppressed insulin levels and poor response to glucagon injection. Hepatoma shows suppressed insulin levels and normal response to glucagon; the latter is indicative of sufficient intact hepatic tissue to store and release glucose and possibly a mediation of hypoglycemia by insulin-like factors (IGFs).

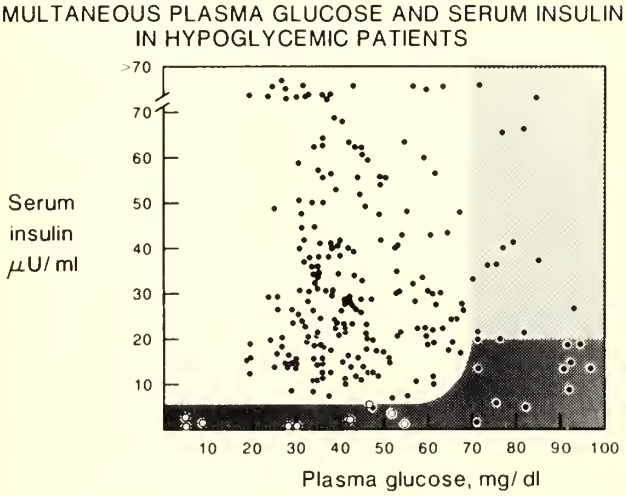

Figure 13.—Simultaneously measured serum insulin and plasma glucose in 72 patients with insulinomas (closed circles) and 6 patients with non-insulin-mediated hypoglycemia (open circles). Ten percent of those with insulinoma for whom multiple simultaneous insulin and glucose determinations were made had insulin values in the normal range during concomitant hypoglycemia. The various shadings reflect differing relationships between simultaneously measured serum insulin and plasma glucose. The darkest shading indicates normal serum insulin concentrations for the full range of plasma glucose. The lighter shading in the upper right portion of the figure shows elevated plasma insulin concentrations in the face of normal plasma glucose concentrations. The quadrant of light shading encompassing serum insulin concentrations from 6 to 25 μU per ml and plasma glucose from 0 to 70 mg per dl depicts plasma insulin concentrations below the upper limit of "normal" at the time of plasma glucose concentrations below the lower limits of normal, the area of greatest difficulty in assessing relative hyperinsulinemia. Probably all of these values are inappropriately elevated because they are above 6 μU per ml. The unshaded portion on the upper left part of the figure shows elevated serum insulin concentrations and depressed plasma glucose concentrations, all of which are consistent with the diagnosis of insulinoma. (Modified from Service FJ and Nelson RL: Insulinoma. Compr Ther 1980; 2:70.)

In a series of 95 patients with insulinoma who underwent diagnostic fasts, Whipple's triad was demonstrated within 12 hours of the last meal in 29%, within 24 hours in 71%, within 36 hours in 79%, within 48 hours in 92%, within 60 hours in 97%, and within 72 hours in 98%.[34] In rare instances, patients with insulinoma may not develop hypoglycemia during prolonged fasting of even up to 96 hours.[34,40] At the time of hypoglycemic symptoms in the group of 90 patients with insulinoma, plasma glucose concentrations were ≤46 mg per dl in 100%, ≤39 mg per dl in 70%, ≤35 mg per dl in 50%, and ≤28 mg per dl in 25%.[34]

The intravenous glucagon test has a diagnostic accuracy of 50% to 80% using criteria of peak insulin ≥130 μU per ml or increase above basal ≥100 μU per ml when conducted after an overnight fast.[41] Hydrochlorothiazide, diphenylhydantoin, and diazoxide may give false-negative responses; tolbutamide, aminophylline, and obesity may give false-positive results.[41] The utility of other tests such as glycosylated hemoglobin, human pancreatic polypeptide, and infusions of alcohol, calcium, epinephrine and propranolol, diazoxide, and somatostatin-tolbutamide in the diagnosis of insulinoma is unproved or inadequate. Human chorionic gonadotropin or one of its subunits may be a marker for functioning malignant insulinomas.[42] Eighty percent of patients with insulinoma may have elevated proinsulin concentrations (>20% of total immunoreactive insulin).[43] Perhaps proinsulin measurements with more modern assays may improve diagnostic accuracy, but these assays are not generally available. In most instances the evaluation of a patient with insulinoma yields unequivocally positive results. On some occasions, however, the data are borderline or even contradictory. In order to make one's way to the correct diagnosis, the reliability of the data needs to be rechecked, the conditions under which they were collected must be ascertained to be proper, and additional corroborating data must be generated.

Localization. Only after the diagnosis of insulinoma has been confirmed biochemically should a localization procedure be done. Pancreatic angiography has been reported to have a high rate of success when stereoscopy, magnification, and subtraction are used[44] (Figure 14). Insulinomas appear as homogeneous, intensely vascular, sharply circumscribed masses within the substance of the pancreas.

Computed tomography has had limited success in localization (Figure 15). Real-time high-resolution ultrasonography done both preoperatively and intraoperatively is currently demonstrating a high degree of accuracy. In a large

series of patients with solitary insulinomas, preoperative ultrasonography successfully localized 63% of the tumors and intraoperative ultrasonography localized 86%[45] (Figure 16). The indications for and value of selective venous sampling for insulin measurement done either by the percutaneous transhepatic route or directly at the time of surgery remain undetermined. Failure to localize an insulinoma should not deter pancreatic exploration in a patient for whom the diagnosis has been firmly established. Surgeons experienced in insulinoma surgery are highly successful in finding the tumor even when it has not been localized preoperatively.[46]

Treatment. Surgical removal is the preferred form of treatment for insulinoma. In a series of 95 patients with insulinoma, 54% of patients underwent successful enucleation of the tumor, 38% partial pancreatectomy, and the remainder a variety of other procedures.[34] In this series, 84% were cured, 7% had diabetes, and the remainder required medical treatment to control persistent hypoglycemia from malignant insulinoma, islet hyperplasia, or a tumor missed during surgery. There was no operative mortality, and the postoperative complication rate was 10%.[34]

Intraoperative glucose monitoring should not be relied upon for surgical management, since there is a high incidence of failure of plasma glucose to increase shortly after successful insulinoma removal.

The median diameter of benign tumors has been reported to be 1.5 cm.[34] Malignant tumors are usually large. Tumors are evenly distributed throughout the pancreas whether benign or malignant, single or multiple. Ectopically located insulinoma and islet hyperplasia are quite rare.[34] The latter is a difficult histologic diagnosis to make and requires quantitative techniques for the establishment of islet number and volume.[47] There is no correlation between the severity of symptoms and size of the insulinoma.[34] Insulinomas have been classified on the basis of the number and type of secretory granules[48] and functional status. Hyperinsulinism from insulinoma appears to be due not to overproduction of insulin but probably to a defect in storage of insulin. Agranular tumors have the highest concentrations of proinsulin.

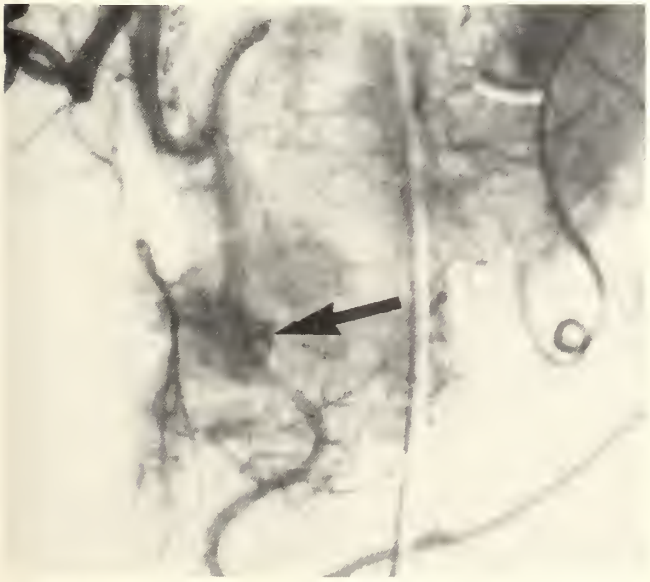

Figure 14.—Celiac axis angiogram: hypervascular tumor **(black arrow)** in the head of the pancreas. (From Stephens DH: Pancreas: Neoplastic lesions, *In* Margulis AR, Burhenne HJ (Eds): Alimentary Tract Radiology, Vol 4. St. Louis, CV Mosby, 1989.)

Treatment of persistent hypoglycemia in a patient with malignant insulinoma, in a patient in whom insulinoma cannot be found at pancreatic exploration, or in one who refuses surgery is best accomplished with diazoxide,[49] which inhibits insulin release, although phenytoin, propranolol, and verapamil have been used successfully in some cases. Long-acting somatostatin analogue has proved useful to control hypoglycemia in some patients with malignant insulinoma. Malignant insulinoma metastasizes primarily to local structures such as regional lymph nodes and liver; distant metastases are uncommon.[50] The chemotherapeutic regimen of choice consists of streptozotocin and 5-fluorouracil.[51] Survival exceeds that recorded for adenocarcinoma of the pancreas.

Factitial and Autoimmune Hypoglycemia

The self-administration of insulin or sulfonylurea may be done covertly by persons with or without diabetes, or these drugs may be administered to an unsuspecting victim or by error.

Figure 15.—Computed tomography scan of the pancreas showing an enhancing tumor **(black arrow).** (From Stephens DH: Pancreas: Neoplastic lesions, *In* Margulis AR, Burhenne HJ (Eds): Alimentary Tract Radiology, Vol 4. St. Louis, CV Mosby, 1989.)

Figure 16.—Intraoperative sonogram showing a 0.8 cm discrete hypoechoic lesion **(black arrow)** within the pancreas between the main pancreatic duct **(open arrow)** and splenic vein **(SV).** (From Gorman B, Charbonneau JW, James ME, et al: Benign pancreatic insulinoma: Preoperative and intraoperative sonographic localization. AJR 1986; 147:929.)

Nondiabetic persons who secretly take insulin or sulfonylureas are predominantly women in the third and fourth decades of life who are employed in health-related occupations.[52] Patients with factitial hypoglycemia have an erratic pattern to the occurrence of symptoms and may tolerate prolonged periods of food deprivation without developing hypoglycemia. With the exception of the unusual cases of insulin autoimmune syndrome and rare detection in insulinomas, the presence of insulin antibodies is strong evidence of repeated injection of insulin. In addition, the presence of low plasma concentrations of C-peptide concomitant with elevated insulin levels and hypoglycemia indicates an exogenous source of insulin (see Figure 12). Insulin antibodies will result in spurious radioimmunoassayable plasma insulin concentrations: very high if the double antibody assay is used and undetectable if the charcoal-coated dextran assay is used. Results of tests for insulinoma (including the C-peptide suppression test if the patient is taking a sulfonylurea)[53] may be indistinguishable between an insulinoma patient and a patient who secretly took the hypoglycemic agent before the test. Concentrations of sulfonylurea should be measured in the plasma or urine if it is suspected of being the hypoglycemic agent. The clinical pattern in diabetic subjects consists of increased frequency of hypoglycemia during treatment and persistence of hypoglycemic episodes after apparent cessation of use of the agent. The presence of insulin antibodies is of no help in the diagnosis in the insulin-treated patient. The rule for the nondiabetic person, that an inverse relationship between C-peptide and insulin levels during hypoglycemia is diagnostic of surreptitious insulin administration, also holds for diabetic patients. If the diabetic patient is deprived of access to the hypoglycemic agent, such as during procedures that require immobilization of both arms or strict confinement to bed or to a seclusion room, hyperglycemia and possibly ketonuria will develop. Insulin has been used for suicide, homicide, and child abuse and by drug addicts. Accidental ingestion of a sulfonylurea has occurred as a result of errors by the patient or by pharmacy or hospital staff.

Autoimmune hypoglycemia comprises two classes of patients, those with insulin antibodies who have apparently never been exposed to exogenous insulin and those with insulin receptor antibodies. The patients with spontaneous generation of insulin antibodies have ranged in age from a few days old to elderly.[54,55] Hypoglycemia may be severe, may occur during fasting or postprandially, and is often self-limited. During episodes of hypoglycemia, plasma free insulin levels have been found to be elevated and plasma free C-peptide concentrations appear to be appropriately suppressed.[56] Distinguishing between insulin antibody autoimmune hypoglycemia and factitial hypoglycemia may be quite difficult. The observation of intermittent production of an abnormal insulin that is immunogenic[57] has not been supported by others.[58] Species-specificity association constants and binding capacities for human, porcine, and bovine insulins of the antibodies from patients with autoimmune hypoglycemia are not different from those of antibodies from insulin-treated diabetics.[56] However, there are sufficient differences in the frequency and duration of insulin administration between patients with factitial hypoglycemia and insulin-treated diabetes to require full characterization of the insulin, proinsulin, and C-peptide antibodies in proven factitial hypoglycemia for comparison with those of the autoimmune hypoglycemic syndrome.[59] Distinction between autoimmune and factitial hypoglycemia by antibody characteristics may become even more difficult now that human insulin has come into common usage. Neither the biochemical characteristics of this syndrome nor the mechanism of the hypoglycemia has been fully elucidated.

Hypoglycemia has been observed in persons with insulin receptor antibodies.[60] During the insulin resistance phase, glucose production rate is excessive and glucose utilization rate is also increased rather than decreased.[61] There are no data on glucose kinetics during the hypoglycemic phase of the disease. Most but not all of the patients with hypoglycemia had preexisting insulin-resistant diabetes and evidence for autoimmune disease before the development of hypoglycemia. Antagonist and agonist action of insulin receptor antibodies may be due to different populations of insulin receptor antibodies that recognize different antigenic sites.[62] This syndrome may respond to glucocorticoid therapy[60] or methyl palmoxinate, an inhibitor of free fatty acid oxidation,[61] but is not corrected by immunosuppressive agents or plasmapheresis.[60]

Non-Beta Cell Tumor Hypoglycemia

A wide variety of tumors of mesenchymal or epithelial origin and some malignant hematologic diseases have been associated with hypoglycemia.[63]

Mesenchymal tumors account for 45% to 64% of the reported cases. Fibrosarcomas, lymphosarcomas, liposarcoma, rhabdomyosarcomas, hemangiopericytomas, leiomyosarcomas, and mesotheliomas constitute the histologic types. The incidence is similar for both sexes. Most tumors occur in the fifth through seventh decades, although they have been observed in the pediatric age range. Tumors associated with hypoglycemia seem to have a predominantly spindle cell morphology. Approximately one third of the tumors are located in the chest and two thirds are in the abdomen, usually in the retroperitoneum. They usually are large and therefore readily detectable.

Hepatomas account for 22% of cases; they are the commonest epithelial tumor to cause hypoglycemia. The incidence of tumor-associated hypoglycemia is greater among Chinese than occidentals. There appear to be two distinct clinicopathologic types: type A is associated with rapidly growing, poorly differentiated cancers in which hypoglycemia is a preterminal event, and type B is associated with well-differentiated and more slowly growing neoplasm in which hypoglycemia occurs early in the course of the disease.[64]

Large adrenal tumors, whether functional or not, may cause hypoglycemia. Hypoglycemia has been associated in rare instances with many other tumor types but not with carcinoma of the lung.

No single pathogenetic mechanism satisfactorily explains all cases of tumor-related hypoglycemia. More than one mechanism may be involved. Metastatic destruction of the adrenals or pituitary and extensive metastatic involvement of the liver can impair glucoregulatory mechanisms. Some tumors evince a high rate of glucose utilization[16] because of a deficient Pasteur effect. In others, substances such as tryptophan metabolites may impair gluconeogenesis. There has not been a convincing documentation of insulin secretion by a non-islet cell tumor, although hyperinsulinemia has resolved after tumor removal in some cases. Although elevated concentrations of insulin-like growth factors (IGFs) have been observed in some patients with non-islet tumor hypoglycemia, there is controversy regarding their role in the pathogen-

esis of the hypoglycemia. The observation that plasma glucose responds to injection of glucagon in hepatoma with hypoglycemia implicates an IGF in the genesis of the hypoglycemia.[65] Proliferation of insulin receptors in insulin-responsive tissues has been reported in one patient with non-islet tumor hypoglycemia.[66] Total or partial surgical removal of the tumor usually results in amelioration of the hypoglycemia.

Hypoglycemia in Hepatic, Renal, and Endocrine Disorders and Miscellaneous Conditions

Symptomatic hypoglycemia is uncommon in liver disease because glucose homeostasis can be maintained with as little as 20% of healthy parenchymal cells, but biochemical hypoglycemia has been reported in a wide variety of acquired hepatic diseases.[67] Abnormalities of the catabolism of many glucoregulatory hormones have been observed in liver disease: glucagon, growth hormone, and cortisol, which would be expected to result in glucose intolerance but not hypoglycemia. During hypoglycemia, plasma insulin concentrations are usually appropriately suppressed. However, hyperinsulinemia may be observed as a result of impaired insulin degradation and/or shunting of portal blood into the systemic circulation. The hypoglycemia of congestive heart failure, sepsis, lactic acidosis, and Reye's syndrome is considered to be due to hepatic mechanisms.

Hypoglycemia is uncommon in adrenocortical insufficiency.[67] Hypoglycemia in hypopituitarism is common in children under six years of age but less so beyond that age.[67] Asymptomatic hypoglycemia has been observed in isolated growth hormone deficiency after prolonged fasting. Spontaneous hypoglycemia has been reported to be a frequent finding in isolated ACTH deficiency. Adults surgically deprived of epinephrine are not subject to hypoglycemia.

Hypoglycemia in nondiabetic persons with renal failure may be due to inadequate gluconeogenic substrate availability.[68] Glucagon deficiency is a theoretic mechanism for hypoglycemia, but the existence of this disorder has not been confirmed.

Hypoglycemia is a concomitant of starvation. It has been observed in persons with protein-calorie malnutrition as a result of anorexia nervosa or extreme food faddism. Inanition may be one of several factors in the genesis of hypoglycemia in patients with multisystem disease and prolonged intravenous fluid therapy. Prolonged, severe exercise may provoke hypoglycemia in untrained persons but is less likely to do so in trained athletes.

Summary

Low plasma glucose concentrations that may or may not be sufficiently low to result in symptoms can be observed as a concomitant of several diverse diseases. Treatment of the primary underlying disorder usually alleviates the hypoglycemia. For patients whose primary symptom is that of hypoglycemia, it is essential to confirm that the plasma glucose concentration is low during the occurrence of symptoms. Symptoms that occur after meals usually are mild and rarely signify serious disease. With rare exceptions, hypoglycemia resulting in major symptoms occurs in the food-deprived state. Lower concentrations of plasma insulin and C-peptide and a concomitant low plasma glucose are major clues to a correct diagnosis.

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Epitomes

Important Advances in Clinical Medicine

Allergy and Immunology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy and immunology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in allergy and immunology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy and Immunology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

New-Generation Antihistamines

HISTAMINE$_1$-RECEPTOR antagonists have been the mainstay of the treatment of various allergic disorders for numerous years. Drowsiness from using traditional antihistamines, an effect attributed to the inhibition of histamine *N*-methyltransferase and the blockage of central histaminergic receptors, has limited the usefulness of this category of medication. In one survey, 62% of patients with significant upper respiratory tract allergy symptoms avoided using an antihistamine for relief because of the resulting sedation. Relatively nonsedating antihistaminic agents have recently become available. These new-generation H_1-receptor antagonists are lipophobic and penetrate the central nervous system to a lesser degree than their first-generation predecessors, thereby greatly decreasing their propensity to sedate. Other advantages of these new antagonists include preferential binding to peripheral H_1 receptors over central ones and the property of possessing minimal antiserotonin, anticholinergic, and α-adrenergic blocking activity.

The present list of second-generation H_1-receptor antagonists includes terfenadine, astemizole, loratadine, cetirizine, and azelastine. Only the first two antihistamines are currently available in the United States. Studies of these new agents reveal the incidence of sedation to be statistically similar to that seen in patients receiving placebo. Subjective and objective methods of assessing sedation and performance have shown that the new-generation antihistamines are a substantial improvement over previously available antihistamines. Other adverse effects of these H_1-receptor antagonists have been reported, however. Terfenadine, at high doses or in combination with other drugs, may have rare cardiotoxic effects. Astemizole may occasionally stimulate the appetite and cause inappropriate weight gain. Large doses of astemizole may also result in cardiac rhythm irregularities. Astemizole binds to peripheral H_1-receptor sites with far greater affinity than any other existing H_1-receptor antagonist. A suppression of histamine-induced wheal-and-flare reactions may still occur in some patients as long as 14 weeks after discontinuing the medication.

Second-generation H_1-receptor antagonists have proved to be effective in decreasing symptoms of sneezing, itching, and nasal discharge, and ocular symptoms in most patients with allergic rhinoconjunctivitis. Challenge studies using intranasal antigen have shown this new category of antihistamines to block or attenuate the immediate reaction to a challenging allergen. Most evaluations show, however, that these agents are no more effective than first-generation H_1-receptor antagonists. The manufacturers recommend the following doses to provide optimal efficacy with a minimal likelihood of causing sedation or other adverse effects: terfenadine, 60 mg twice a day; astemizole, 10 mg daily; loratadine, 10 mg daily; cetirizine hydrochloride, 10 mg daily; and azelastine hydrochloride, 4 mg per day. Although studies comparing these new agents are limited, there is some information to suggest that terfenadine relieves symptoms more rapidly than astemizole, but astemizole may have a longer duration of action than the other new agents.

There is some interest in applying these new H_1-receptor antagonists topically to the nasal mucosa and conjunctivae. Studies using intranasal azelastine have shown substantial protection against allergen-triggered rhinitis and allergic conjunctivitis. These new agents may have antiallergic properties different from their H_1-blocking activity. That is, they may decrease the release of inflammatory mediators such as histamine and prostaglandin D_2 from mast cells and basophils, a property different from the simple antagonism of H_1 receptors. Because of these antiallergy properties, second-generation antihistamines have also been studied for beneficial effects in the treatment of asthma. Under controlled conditions in the laboratory, some of these new antagonists have clearly had a protective effect against bronchospasm induced by allergens, exercise, histamine, or cold air. Further studies are underway to investigate their possible beneficial effects in patients with asthma. Second-generation H_1-receptor antagonists have also been used in the treatment of chronic idiopathic urticaria, and results show them to be well tolerated and efficacious in modifying urticaria symptoms.

MICHAEL J. WELCH, MD
San Diego, California

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Penicillin Allergy

For more than 50 years, the penicillins have been among the most useful antibiotics available for the treatment of human infections. The use of the penicillins and other β-lactam antibiotics has been limited, however, by relatively high rates of allergic reactions among patients and the failure of physicians adequately to identify those patients who are at risk for such reactions. Treatment courses with penicillins are complicated by hypersensitivity reactions in as many as 10%, anaphylactic reactions in 0.01%, and fatal reactions in 0.0015%, or about 1 per 50,000 treatment courses.

Identification of the immunologic metabolites of penicillin has enabled a prospective identification of many patients at risk for systemic or potentially fatal type 1 immediate (IgE-mediated) hypersensitivity reactions to these antibiotics. In vivo, a small portion of administered penicillin is metabolized to biochemically active compounds that can covalently bind to plasma proteins and elicit immunologic responses. The penicilloyl product is the most abundant metabolite, accounting for 95% of protein-bound drug metabolites, and is thus termed the "major determinant." This determinant is commercially available for skin testing. Three other penicillin metabolites, termed the "minor determinants," consisting of penicillin, penicilloic acid, and penilloic acid may play an important role in penicillin allergy. Although not currently available commercially, they have been synthesized in several laboratories at academic centers.

Skin testing is simple, sensitive, and specific for predicting immediate-type hypersensitivity reactions to the penicillins. When testing is done by trained personnel, patients with a history of an adverse reaction to penicillin and negative epicutaneous and intradermal skin tests with major and minor determinants (and appropriate positive and negative controls) have less than a 1% risk of a subsequent IgE-mediated systemic reaction. Skin test reactions to any of the penicillin determinants carries about a 70% chance of systemic reactions when the drug is subsequently administered. The sensitivity of testing with the penicilloyl (major) determinant alone is only 76%, whereas the sensitivity of testing with the penicilloyl and benzylpenicillin determinants is approximately 93%.

In the absence of available minor determinants, physicians have relied on the clinical history alone and the availability of alternative antibiotics. In one report, only 10% of patients with a history of penicillin allergy were found to have positive skin tests with both the major and minor determinants. As many as 90% of patients are thus unnecessarily deprived of a highly effective, nontoxic, often less expensive class of antibiotics. Some practitioners have suggested using "old" aqueous penicillin for skin testing, erroneously thinking that the aging process will lead to the formation of hydrolysis products that will cross-react with minor determinants; this is an unacceptable practice. It is hoped that the penicillin minor determinants will be commercially available in the near future.

Although cross-reactivity between cephalosporins and penicillin has been shown in many animal systems, the true in vivo incidence of such cross-reactivity is not known. Cephalosporin skin testing is limited to the native drug because the relevant degradation products are unknown, but the use of the native drug alone appears to have little predictive value. Ongoing prospective studies suggest that the incidence of cross-reactivity is probably low, but more accurate determination is needed. In studies to determine the level of allergic cross-reactivity between the monobactam antibiotics and the penicillins, there was no evidence of immunologic cross-reactivity. Moreover, to date, patients with a history of true IgE-mediated penicillin reactions have had no adverse reactions from monobactam antibiotics. Studies have also been conducted comparing skin test reactivity between the penicillin determinants and the major and minor determinants of the carbapenam antibiotic, imipenem. A high degree of cross-reactivity between the minor determinants of penicillin and the analogous determinants of imipenem was found, suggesting that this drug should be given to penicillin-allergic persons with the same degree of caution as if the patients were to receive penicillin.

DANIEL ADELMAN, MD
San Francisco, California

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Points to Consider in the Care of Patients Infected With the Human Immunodeficiency Virus

As human immunodeficiency virus (HIV) disease is recognized more as a progressive chronic illness, primary care practitioners will be assuming more responsibility for the care of these patients. Practitioners need to be familiar with the initial staging of the disease, current health maintenance recommendations, and prophylaxis and treatment regimens.

The initial staging of HIV infection relies on the patient's history, pertinent physical findings, the CD4:CD8 cell ratio, and the absolute CD4 and CD8 cell counts. A history of opportunistic infections, malignant neoplasms, or wasting symptoms is important, but a history of tuberculosis, syphilis, or herpes simplex or zoster infections should also be obtained. A thorough travel history is important because disseminated coccidioidomycosis or histoplasmosis can be the initial presentation of an HIV-infected patient from an endemic area.

The initial physical examination should emphasize those findings that define the acquired immunodeficiency syndrome (AIDS) or the AIDS-related complex. The early signs of HIV dementia in particular can be subtle.

Once a person tests positive for HIV antibodies, laboratory studies should include a complete blood count, a chemistry panel, and T-cell subsets. Serologic tests should include a hepatitis panel, rapid plasma reagin (RPR) or VDRL, and a *Toxoplasma* titer. A standard purified protein derivative (PPD) and a control skin test should be administered. In asymptomatic patients, the T-cell subsets and complete blood count should be repeated every three to six months. The chemistry panel should be repeated every six months or more frequently if symptoms develop or if the patient is taking a hepatotoxic medication. The RPR and PPD tests should be repeated annually. Vaccinations have been found to be variably effective in HIV-infected persons: the pneumococcal vaccine should be given once, a conjugate influenza

vaccine annually, and hepatitis B vaccine if results of the hepatitis panel are negative.

The only anti-HIV therapy that is approved by the Food and Drug Administration at this time is zidovudine (AZT). This nucleoside analogue selectively inhibits HIV type 1 reverse transcriptase activity and viral replication. Two recent clinical trials have shown that the development of AIDS or severe AIDS-related complex is substantially delayed in patients taking AZT. In addition, the use of AZT has been shown to have significant therapeutic effects in patients with AIDS dementia. It is generally recommended to begin AZT therapy in all HIV-infected patients with CD4 counts of less than 0.5 cells $\times 10^9$ per liter (500 cells per μl). Some argue that this increases the risk of drug resistance developing, however. Recent clinical trials have shown that decreasing the dose from 1,500 mg per day to 500 mg per day (100 mg every four hours) offered asymptomatic patients clinical benefit with substantially fewer toxic effects. Another dideoxynucleoside analogue, dideoxyinosine (DDI), is presently undergoing a clinical stage II-III trial. Studies show it has potent anti-HIV activity, but it also has significant toxicity, some of its effects including peripheral neuropathy and pancreatitis.

The US Public Health Service recommends *Pneumocystis carinii* pneumonia prophylaxis for all patients with CD4 counts of less than 0.2 $\times 10^9$ per liter (200 per μl). The combination drug, trimethoprim-sulfamethoxazole, 5 mg per kilogram per day in a divided dose for three days a week, is one regimen. Unfortunately, there is a relatively high incidence of sulfa sensitivity in patients with AIDS. The use of dapsone, 50 mg per day, is an acceptable alternative that has not been studied as carefully. Aerosolized pentamidine given as a 300-mg dose every month was shown to decrease the number of episodes of *P carinii* pneumonia and prolong survival. There have been a few reports of extrapulmonary *P carinii* in patients receiving aerosolized pentamidine treatments. Pulmonary relapses in this population tend to be in the upper lobes.

Mycobacteria, both typical and atypical forms, have a strong association with HIV infection. The Centers for Disease Control recommend that any HIV-positive person, regardless of age, who has a positive PPD skin test (5 mm of induration) take isoniazid, 300 mg per day, for about a year. Currently there is no accepted prophylactic regimen for atypical mycobacteria.

Recurrent herpes simplex virus 1 and 2 and herpes zoster infections can be prevented with the use of acyclovir, 200 mg three to four times a day. The routine use of acyclovir or ganciclovir in an effort to prevent symptomatic cytomegalovirus infection is not recommended.

Persons infected with HIV who have a positive RPR or VDRL should have a lumbar puncture study done. If the cerebrospinal fluid (CSF) is normal, the patient may be treated with 2.4 million units of penicillin G benzathine given intramuscularly weekly for three weeks. If there are typical symptoms of neurosyphilis or if the CSF VDRL is positive for syphilis, treatment should be started. Many HIV-infected persons have an increased CSF protein concentration and pleocytosis, so these findings alone do not implicate neurosyphilis.

Human immunodeficiency virus disease should be considered a progressive, chronic process. Primary care practitioners need to lay the foundation for the care of HIV-positive patients. Patients can manifest a spectrum of diseases, many of which may now be preventable. Checking serial CD4 counts and getting careful interval histories and physical examinations will enable physicians or allied health care practitioners to stage the disease and plan appropriate maintenance measures.

JANE T PURSER, MD
GILDON BEALL, MD
Torrance, California

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Harmful Health Effects of Passive Smoking

ALTHOUGH THE ROLE of direct cigarette smoking in chronic diseases including lung cancer and heart disease has been well established, scientific evidence has only recently implicated the indirect inhalation of cigarette smoke as a risk factor for disease as well. Since the Surgeon General's 1986 report on involuntary smoking, several hundred scientific articles have reported the harmful effects of environmental tobacco smoke. The Environmental Protection Agency recently called environmental tobacco smoke "one of the most widespread and harmful indoor air pollutants."

The strongest evidence linking passive smoking to increased disease prevalence exists in children. Even in temperate climates, children spend about two thirds of their time indoors, placing family members living with smokers at increased risk. It is estimated that 70% of all children in the United States are exposed to the hazards of cigarette smoke for much of their developmental years. During the first year of life, pneumonia and bronchitis appear with greater frequency in infants with exposure to cigarette smoke. There is also an increased incidence of otitis media, bronchitis, acute exacerbations of asthma, and reduced lung function in children whose parents smoke. Cough and mucus production occur more frequently among children of smokers. These clinical problems often have a dose-response relationship whereby the more cigarettes per day the parents smoke, the more likely a child is, for example, to require asthma medications. In addition, an increased serum immunoglobulin E level and an increased prevalence of eosinophilia have been seen among children of smoking parents. This may explain in part the increased frequency of respiratory symptoms in children of smoking parents. Furthermore, children whose parents smoke are twice as likely to become smokers themselves, additionally jeopardizing their health in later life.

The risk of environmental tobacco smoke to adults has not been examined extensively and is therefore not conclusive. One startling finding is that passive smoking is associated with a higher risk of lung cancer in nonsmokers. The National Academy of Sciences (1986) estimated that 3,800 lung cancer deaths each year in the United States are caused by passive smoking. Studies examining respiratory symptoms in adults with exposure to secondhand smoke have shown conflicting results, as have others examining lung function and clinical exacerbations of asthma. Those living with smokers are not the only ones at risk. A health insurance survey concluded that almost two thirds of nonsmoking adults had

some exposure to passive smoke, most often in places outside the home. Testing for urinary or salivary levels of cotinine, a by-product of cigarette smoke, has documented the presence of tobacco smoke exposure in a large proportion of the general population.

Secondhand smoke is now recognized as a health threat in this country. This has caused a dramatic change in public attitudes regarding the rights of the smoking minority versus the welfare of the nonsmoking public. Further research is needed to determine more precisely how great the risk is from this exposure.

SUSAN B. MELTZER, MPH
ELI O. MELTZER, MD
San Diego, California

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Immunoglobulin G Subclasses

THE FOUR IMMUNOGLOBULIN (Ig) G subclasses are products of discrete constant region genes encoded within the immunoglobulin heavy-chain locus on chromosome 14. Each immunoglobulin represents the expression of several rearranged variable region genes with one constant region gene producing a single polypeptide chain. The finished immunoglobulin molecule is a four-chain structure composed of two identical heavy chains coupled to two identical light chains (κ or λ) encoded on chromosomes 2 and 22, respectively. Monoclonal antibody and recombinant genetic technology have resulted in major advances in understanding immunoglobulin structure-function relationships as well as accurate methods for measuring IgG subclasses and specific antibodies to defined antigens.

Studies of purified isolates of human IgG subclasses, or genetically constructed antibodies of identical variable regions (idiotype) but different constant regions (isotype), have supplemented and clarified earlier studies of naturally occurring antibodies. These studies confirm major effector differences in IgG subclass antibodies. IgG3 is more efficient than IgG1 in activating complement, but IgG2 is minimally active and IgG4 is inactive. IgG1 is more efficient than IgG2 in enhancing human complement-mediated killing of some bacterial pathogens. IgG4 is functionally univalent and does not form large latticed immune complexes. Although these differences may have clinical implications, extrapolation from in vitro studies to defense capabilities in vivo may be misleading because of the physiologic redundancy of defense mechanisms.

Minor IgG subclass deficiencies have been linked to an increased susceptibility to infection. Often IgG2 or IgG2 to IgG4 deficiency occurs along with IgA deficiency. The strongest disease association has been that of low IgG2 levels and recurrent infection with encapsulated bacteria such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae*. The clinical implications of low IgG subclass levels are not well understood, however. Healthy persons lacking constant region genes for one or more IgG subclasses have been identified; healthy blood donors with variable IgG subclass deficiencies have also been found; persons with initially low IgG subclass levels can correct over time; and, finally, normal IgG subclass levels but deficient specific antibody responses have been described in persons with recurrent infection. Thus, IgG subclass deficiencies are likely markers of broader immune abnormalities rather than inherent causes of disease. The best understood example of this is also IgG2 deficiency. Low IgG2 levels in patients with recurrent infection are associated with an inability to respond to bacterial polysaccharides, but in healthy IgG2-deficient persons, normal antibody responses are seen. This suggests that the primary defect is specific immune responsiveness to bacterial polysaccharides; if impaired, low IgG2 levels are frequently but not invariably found. Therefore, the assessment of recurrent sinopulmonary or systemic pyogenic infection—the major indication for evaluating IgG subclasses—should include both IgG subclass levels and specific antibody responses to protein and polysaccharide antigens, including the paired measurement of serum before and four weeks after immunization with capsular vaccines such as unconjugated *H influenzae* type b and pneumococcal polysaccharide vaccine. Age-related interpretation is essential because healthy infants and toddlers may not respond to these vaccines. At present, IgG subclass-specific antibody assays are not generally available. An IgG subclass deficiency associated with impaired antibody responses can be treated with intravenous immune globulin if conservative measures such as antibiotic prophylaxis are ineffective. The use of intravenous immune globulin therapy in patients with an IgG subclass deficiency without a demonstrably impaired antibody response is controversial; many clinicians await the results of a multicenter controlled trial now in progress.

An analysis of IgG subclass levels must take into account their non-Gaussian distribution, wide normal ranges, and ethnic differences. Allelic population differences in certain heavy- and light-chain regions (allotypes) can affect IgG subclass levels and specific antibody responses. For example, whites with the IgG2m(n) allotype have higher IgG2 levels and antibody responses to bacterial polysaccharides than persons lacking this allele. Adult levels of IgG1 and IgG3 are attained earlier than levels of IgG2 and IgG4. For IgG3 and especially for IgG4, true deficiencies are hard to establish, given that low levels are found in many normal younger children.

Generally, antibody responses to protein antigens—such as viral envelopes—mainly involve IgG1 and IgG3. Antibody responses to capsular polysaccharides seem to fall into two groups, those eliciting greater IgG2 isotype restriction such as *S pneumoniae* and those with a lesser degree of IgG2 restriction such as *H influenzae* or meningococcal types A and C, where substantial IgG1 responses may occur. Finally, antibody responses to protein antigens presented repetitively, such as allergen extracts used in hyposensitization therapy, are largely restricted to IgG1 and IgG4, with the latter often predominant.

RICHARD B. MOSS, MD
Palo Alto, California

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Eosinophilia-Myalgia Syndrome

THE PRESENCE OF PERIPHERAL EOSINOPHILIA (an absolute eosinophil count of greater than 0.35×10^9 per liter [350 per μl]) provides a clue to an underlying allergy, parasite infection, the pulmonary infiltrates and eosinophilia syndrome, a neoplasm, vasculitis, an immunodeficiency state, an idiopathic hypereosinophilic syndrome, or a drug reaction. The diagnosis of a drug reaction is usually based on the response to removing the drug and the exclusion of other possible diagnoses, as drug reactions have no pathognomonic clinical or laboratory findings. The association of the eosinophilia-myalgia syndrome (EMS) with the ingestion of the amino acid tryptophan is a striking, newly recognized example of a drug reaction associated with eosinophilia. In response to this association, the Food and Drug Administration banned all over-the-counter sales of tryptophan in December 1989.

The current surveillance definition of EMS used by the Centers for Disease Control (CDC) requires the fulfillment of three criteria: an eosinophil count of greater than 1×10^9 cells per liter (1,000 cells per μl), incapacitating myalgias, and the exclusion of other infectious and neoplastic causes. In addition to the prominent muscle involvement (myalgias and muscle tenderness), other organs involved in EMS include the skin (edema of the skin, transient maculopapular or urticarial rash and late morphealike lesions), lungs (dyspnea, cough, hypersensitivity pneumonitis), heart (palpitations, myocarditis), joints (arthralgias), and peripheral nerves (paresthesia). Although creatine kinase levels are usually normal, aldolase levels are frequently elevated, and a muscle biopsy specimen shows perivascular infiltrates of eosinophils and mononuclear cells. Patients with EMS have degranulated eosinophils in affected tissues, widespread activation of collagen gene expression in dermal fibroblasts, and increased tryptophan metabolism by way of the kynurenine pathway.

Available in the United States since about 1974 as a dietary supplement without prescription, tryptophan has been a popular remedy for insomnia, the premenstrual syndrome, depression, and loss of weight. Average patient doses of tryptophan range from 1 to 5 grams per day. In comparison, single servings of meat, fish, poultry, and some cheeses contain more than 200 mg of tryptophan. Tryptophan is metabolized by way of hydroxytryptophan to serotonin or by an alternative pathway to kynurenine. Because tryptophan is an essential amino acid, the presence of a contaminant or impurity in tryptophan products has been postulated to be responsible for the syndrome. In Minnesota, an analysis of the epidemiology of EMS has revealed that the outbreak of EMS was associated with the consumption of tryptophan manufactured by one of six manufacturers providing tryptophan to US consumers before December 1989. Even though the purity of tryptophan in the company's manufacturing process was at least 99.6%, a trace contaminant formed after a chemical reaction between two tryptophan molecules and acetaldehyde (1,1′-ethylidenebis [tryptophan]) has been associated with the risk of EMS developing.

At least 19 deaths and more than 1,400 cases of severe inflammatory disease due to EMS have been reported to the CDC. While the current CDC surveillance criteria for the diagnosis of EMS may exclude patients with milder forms of the syndrome, caution should still be exercised in diagnosing EMS in patients without eosinophilia because various rheumatic diseases, including fibrositis, polymyalgia rheumatica, and systemic sclerosis, may produce similar clinical manifestations. Therefore, the diagnosis of EMS in patients with milder myalgias, lower eosinophil counts, or other features suggestive of EMS requires clinical judgment and the appropriate weighing of all available clinical, laboratory, and, where indicated, muscle biopsy information. Because the only clear-cut recommendation for therapy (to stop ingesting tryptophan) has already been made, the use and the duration of other therapies, such as glucocorticoids, needs to be tailored to each patient, depending on the severity of the disease and risk-benefit considerations.

Although further studies may provide important insights into the cellular mechanisms of action of the postulated trace contaminant responsible for EMS, the identification of tryptophan as the etiologic agent associated with the development of EMS and its prompt removal from the over-the-counter market has prevented EMS from becoming an even greater public health concern.

DAVID H. BROIDE, MB, ChB
San Diego, California

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Asthma Without Wheezing

ASTHMA IS A DISORDER characterized clinically by episodes of wheezing, dyspnea, cough, and chest tightness. Spirometry shows reversible airways obstruction, but asthma may present with dry cough as its sole manifestation. This form of asthma has been variously termed "hidden," "atypical," "variant," or "cough-type" asthma. It appears to be a distinct disorder and is characterized by a dry, repetitive cough occurring during waking as well as sleeping hours that may be exacerbated by respiratory viral infections, exercise, and cold air. Frequently members of the immediate family have a history of allergy. Although found in all ages, atypical asthma is thought to be among the most common causes of chronic cough in childhood.

The cough of asthma is unresponsive to antitussives, antibiotics, and antihistamines, but it usually responds to a course of bronchodilators or corticosteroids. Routine spirograms may be normal. The diagnosis can be confirmed by a positive methacholine or exercise challenge test. The bronchial hyperresponsiveness evidenced by these tests is mostly reversed by the use of bronchodilators. In time, many patients have progression to typical asthma. In the differential diagnosis, other sources of cough should be considered, including the central nervous system and the pulmonary interstitium. Conditions such as pertussis, psychogenic cough, cystic fibrosis, sinusitis, and drug reactions are usually readily excluded.

One reason cited for cough without wheezing is that cough receptors are separate from the irritant receptors, which are responsible for wheezing. In one study the predominance of cough in a group of patients with asthma was attributed to cough receptors stimulated in the trachea and

large bronchi where their number exceeds those in the smaller airways. In addition, mediators of asthma may have selective effects on the bronchial cough receptors.

Some authorities suggest that wheezing is present subclinically and would be uncovered with careful auscultation after maximal forced expiration. Wheezing after such maneuvers could not, however, be correlated with tests of bronchial hyperresponsiveness in a group of patients diagnosed as having atypical asthma.

Recognizing this form of asthma is important because the disorder responds readily to the use of bronchodilators in most patients and to corticosteroids in the rest.

HAROLD NOVEY, MD
Irvine, California

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Chronic Granulomatous Disease

CHRONIC GRANULOMATOUS DISEASE (CGD) is a rare inherited disorder characterized by recurrent pyogenic infections most commonly involving the lung, liver, lymph nodes, or deep subcutaneous tissues. Chronic inflammation often develops, and complications due to obstructive granuloma, fibrosis, bronchiectasis, and emphysema may occur. Chronic granulomatous disease occurs because of an inability of phagocytic cells to convert oxygen into superoxide (O_2^-). The killing of ingested microbes is impaired because O_2^- is the precursor for all other microbicidal oxidants produced by phagocytic cells. The microorganisms most frequently responsible for infections in CGD include *Staphylococcus aureus*, *Enterobacter* species, and aspergilli.

An enzyme referred to as the respiratory burst oxidase is normally responsible for the generation of O_2^- and is defective in patients with CGD. The nitroblue tetrazolium (NBT) test remains the most common method to diagnose CGD. This test is based on the ability of O_2^- to reduce NBT from a yellow water-soluble tetrazolium dye to a blue insoluble formazan pigment that is easily visible under light microscopy as intracellular precipitates within activated neutrophils and monocytes. Recently it has become apparent that the oxidase is actually a complex multicomponent enzyme system that includes several cytosolic components and a unique heterodimeric membrane-bound cytochrome *b*. It is therefore not surprising that CGD, like many other inherited diseases, is a heterogeneous group of disorders, each with a different genetic defect affecting a separate component of the oxidase.

The discovery of a method to activate the oxidase in a cell-free system has made it possible to classify CGD into oxidase defects involving either the membrane or cytosol. Most patients with CGD (55% of cases) have a membrane defect due to abnormalities in the 91-kd glycoprotein subunit of the cytochrome *b*. The gene encoding this protein is located within the p21 locus of the X chromosome, and mutations at this site are responsible for the classic X-linked form of CGD. In 5% of cases, a membrane defect occurs due to an inherited abnormality in the 22-kd subunit of the cytochrome *b*, which is encoded by a gene on chromosome 16. No patients with CGD have been reported to have membrane defects other than abnormalities involving cytochrome *b* subunits. Patients with CGD who have cytosol defects (35% of cases) usually lack a 47-kd phosphoprotein. This protein is critical in the translocation of known cytosolic oxidase components to the membrane where the active oxidase resides. In 5% of cases, the CGD phenotype results from a deficiency of another cytosol oxidase component, a 67-kd polypeptide of unknown function. So far, all CGD patients with known cytosol defects have abnormalities involving either the 47-kd or 67-kd cytosolic proteins. Inheritance for both is autosomal recessive; the 47-kd and 67-kd proteins are encoded by genes on chromosomes 7 and 1, respectively. The exact nature of the genetic defects causing these types of CGD remains unknown. Asymptomatic carriers of these cytosol defects can be identified using the cell-free system.

The cornerstones of therapy for CGD remain daily antibiotic prophylaxis, the early institution of parenteral antibiotic therapy, and the prompt surgical drainage of abscesses. Although no controlled trial has been done, extensive clinical experience has shown that antibiotic prophylaxis in patients with CGD reduces the incidence of infections and prolongs patients' survival. Recombinant human interferon gamma (IFN-γ) can now also be included as an effective and safe form of prophylactic therapy for patients having CGD. In a recently reported double-blind placebo-controlled study of 128 patients with CGD, recombinant IFN-γ therapy (0.05 mg per m^2 per dose given subcutaneously three times a week) led to a 70% reduction in the incidence of serious infections. Recombinant IFN-γ therapy was particularly beneficial in children younger than 10 years. The treatment was well tolerated in patients of all ages, and many patients treated for more than two years have yet to experience serious toxic effects. The clinical response to recombinant IFN-γ therapy occurred in all forms of CGD, regardless of the genetic defect, and was not associated with any improvement in phagocyte O_2^- production. The precise mechanism(s) of action of recombinant IFN-γ in CGD remains unknown; it appears that it enhances host defenses through a pathway other than phagocyte O_2^- production. Currently it is recommended that recombinant IFN-γ, three times a week, and daily antibiotic prophylaxis be given together indefinitely.

Based on the current understanding of the oxidase, it appears that somatic gene therapy directed at autologous marrow stem cells may eventually become a promising treatment of CGD. Further characterization of the oxidase also has important implications for disorders other than chronic granulomatous disease. It is anticipated that in the near future, agents that modify oxidase activity will become important anti-inflammatory drugs.

RICHARD C. WOODMAN, MD
Calgary, Alberta, Canada

JOHN T. CURNUTTE, MD, PhD
La Jolla, California

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New Uses of Intravenous Immune Globulin Therapy

ALTHOUGH THE MAIN INDICATION for intravenous immune globulin (IGIV) is the treatment of primary immunodeficiencies, recent studies have shown a role for IGIV in treating selected secondary immunodeficiencies and autoimmune diseases.

Secondary immunodeficiency occurs in previously immunocompetent persons as a result of another disorder. Such disorders include prematurity, thermal and blunt trauma, leukemia, bone marrow transplantation, and human immunodeficiency virus (HIV) infection.

Data from several recent studies indicate a decreased risk of group B streptococcal infections in premature infants treated prophylactically with IGIV. Further studies are being done to help better define guidelines for the use of IGIV in these infants. Bone marrow transplant recipients treated with IGIV have reduced rates of septicemia and a decreased incidence of graft-versus-host disease compared with untreated controls. Intravenous immune globulin is also effective in decreasing serious bacterial infections in patients with chronic lymphocytic leukemia and hypogammaglobulinemia. Severe head trauma is associated with diminished antibody responses, and, because of this, the usefulness of IGIV in pediatric head trauma is currently under study.

Initial uncontrolled studies suggest a role for IGIV in patients with the acquired immunodeficiency syndrome, especially in young children who are antibody deficient and lack memory B cells. Until the results of controlled trials are available, the use of IGIV in patients with HIV infection remains controversial.

The treatment of both acute and chronic immune thrombocytopenic purpura with IGIV is now well established. This success has led to the investigation of its use in other autoimmune disorders. High doses of IGIV given within ten days of the start of Kawasaki's disease have been shown to decrease the incidence of coronary aneurysms and to reduce fever and acute inflammation. Recent studies have shown that a single large dose of IGIV, 2 grams per kilogram, is as effective as the previously recommended smaller daily dose given over four days. Other autoimmune diseases treated with IGIV include autoimmune hemolytic anemia, autoimmune neutropenia, myasthenia gravis, lupus erythematosus, rheumatoid arthritis, bullous pemphigoid, and diabetes mellitus. Most of the reports to date are anecdotal or are of preliminary uncontrolled trials.

The mechanism of IGIV action in autoimmune disease remains unknown. There is evidence in immune thrombocytopenic purpura that one mechanism may be Fc-receptor blockade. In Kawasaki's disease, the use of IGIV suppresses polyclonal immunoglobulin synthesis and T-cell activation. Another possible mechanism is immune network modulation by anti-idiotype antibodies present in IGIV. Elucidating the mechanism of this agent in these disorders will provide insight into the primary disorder itself that perhaps will lead to more specific and less costly therapies.

NEVIN W. WILSON, MD
La Jolla, California
JOHN F. BASTIAN, MD
San Diego, California

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Alerts, Notices, and Case Reports

Feline-Transmitted Sporotrichosis in the Southwestern United States

JOSEPH CARAVALHO, Jr, MD
Ft Benning, Georgia

JAMES B. CALDWELL, DO
BENNETT L. RADFORD, DO
AVA R. FELDMAN, DO, JD
El Paso, Texas

SPOROTRICHOSIS is a chronic disease caused by a single species of fungus, *Sporothrix schenckii*. Although considered ubiquitous, *S schenckii* is most commonly found along coastal regions and river valleys of the southern United States and in countries with similar climates.[1] The usual mode of infection is by wound contamination or accidental inoculation, and it is characteristically felt to be an occupational hazard of farmers and florists.[2] The zoonotic potential of *S schenckii* has been reported with birds, dogs, horses, and rats.[3] More recent reports have implicated the cat as a source of disease transmission, thus placing veterinarians and owners of infected pets at increased risk.[4]

Recently a patient residing in the southwestern United States presented with a digital ulcer and tender nodules with lymphocutaneous spread. *S schenckii* was cultured from both the patient and his cat. The findings in this patient serve to highlight an unusual disease transmission and problems in diagnosis. In addition, we review the medical literature on sporotrichosis.

Report of a Case

The patient, a 29-year-old man, was referred to William Beaumont Army Medical Center, El Paso, Texas, for evaluation of a nonhealing ulcer on the dorsum of his left thumb associated with tender nodules extending along the ventral forearm, arm, and axilla of one month's duration. The patient noted a "small wart" on the dorsum of the left thumb overlying the interphalangeal joint about two months before admission that subsequently ulcerated. Painful nodules developed in a linear pattern along his forearm, arm, and axilla. He had no constitutional symptoms associated with this ulcer. Before admission, he was seen on several occasions by his primary care physician and treated for an infectious process with successive courses of penicillin, erythromycin, and tetracycline antibiotics.

The patient did not garden or care for aquarium fish, but he did recall walking through open fields several weeks before the initial papule. He had no recollection of cuts or abrasions, but he acknowledged taking in a stray cat about three months before admission. The cat was found on a desert roadside and had a moist ulcerative lesion along its upper lip. The patient was principally responsible for its care, which involved changing its bedding and caring for its wound.

The patient was afebrile and appeared well. On physical examination, he had a 2-cm well-demarcated, nontender ulcer with erythematous raised borders and a purulent base extending from the proximal nail fold to the midproximal phalanx of the dorsum of the left thumb (Figure 1). There were multiple subcutaneous nodules extending from the ulcer proximally along the medial forearm and distal arm (Figure 2). The epitrochlear nodes were spared, but a 1.5-cm tender left axillary node was palpable.

Laboratory studies, including a complete blood count, Westergren sedimentation rate, SMA-20 chemistry panel, antinuclear antibody and rheumatoid factor titers, rapid plasma reagin test, and human immunodeficiency virus antibody test were all unremarkable. Roentgenograms of the chest and left upper extremity were within normal limits.

Punch biopsies were taken from the leading edge of the ulcer and from a discrete nodule. Sections of the formalin-fixed biopsy specimen stained with hematoxylin and eosin, Gram's, and acid-fast techniques showed deep and superficial acute and chronic perivascular and periadnexal inflammation with focal erythrocytic extravasation. Periodic-acid Schiff and methenamine-silver stain preparations revealed spores suggestive of *S schenckii*. Aerobic and anaerobic tissue cultures showed no growth. Tissue inoculated on Sabouraud's dextrose agar grew mycelial colonies morphologically consistent with those of *S schenckii* (Figure 3). Transfer culture using brain-heart infusion media revealed oval, round, and cigar-shaped budding yeast that were compatible with *S schenckii*. Potato dextrose agar slide culture showed thin, delicate hyphae and conidial clusters diagnostic for *S schenckii* (Figure 4). Culture of a specimen of the feline's perioral ulcer also revealed *S schenckii*.

A regimen of oral potassium iodide drops, three times a day, was started. The patient tolerated this well, and over a course of seven days, therapy was increased from 5 to 40 drops three times a day by 5-drop increments per dose. He had slow but continuous improvement, with complete resolution within two months of treatment. Therapy was continued for four weeks following the clinical resolution. His cat was also started on potassium iodide therapy, with slowly progressive resolution.

Discussion

Sporotrichosis is an indolent fungal infection of both humans and animals caused by the dimorphic *Sporothrix schenckii*. Formerly known as *Sporotrichum schenckii*, it was first described by Schenck in 1898.[5]

This saprophytic fungus is found as a mold on decaying vegetation, soil, and timber. Although considered ubiquitous, it is most commonly found along waterways of the southern United States and in areas of the world with similar climates such as Mexico and other Latin American countries where it is the most common cause of deep cutaneous mycosis.[6] The warm arid environment of the southwestern United States is an uncharacteristic location for *S schenckii*.

Infections are typically caused by accidental inoculation (Table 1), with puncture wounds usually incriminated. Tra-

(Caravalho J Jr, Caldwell JB, Radford BL, Feldman AR: Feline-transmitted sporotrichosis in the southwestern United States. West J Med 1991 Apr; 154:462-465)

From the Department of Medicine, William Beaumont Army Medical Center, El Paso, Texas. Dr Caravalho is now at Ft Benning, Georgia.

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Reprint requests to Major Joseph Caravalho, Jr, USAMEDDAC, PO Box 56100, Ft Benning, GA 31905-6100.

ditionally, those working with plants and agriculture as well as timber are felt to be at increased occupational risk. There is otherwise no specific predilection for race, age, or sex. Natural infections among animals have been identified in rats, dogs, birds, horses, and cats. A similar mode of infection has been described for these animals.[7] Among cats, a larger proportion of males have been reported infected, due in part to their propensity for aggressive outside activity.[8]

Recently the zoonotic potential of infected cats has been reported, placing veterinary providers and pet owners at increased risk of disease.[4] Cats are thought to be an important human health risk in this regard, based on the notably large number of organisms retrievable from infected sites. They appear to shed fungi continuously from both wound and feces, thus predisposing humans to both transcutaneous and respiratory inocula.[9] There remain only sporadic reports of other zoonotic and person-to-person transmission.[3,10,11]

Although cutaneous trauma is essential for most infections, this history is generally absent. Some authors think that mildly abraded skin is all that is needed for feline-to-person transmission because of the cat's highly contagious nature.[9] The characteristic history, therefore, begins with the primary lesion at the site of injury. This may be a papule, pustule, nodule, abscess, or verrucous growth with variable tenderness.[1]

TABLE 1.—*Characteristics of Sporotrichosis*

History
- Accidental *Sporothrix schenckii* inoculation: rose thorns, spiders, sphagnum moss, animal bites, or scratches
- Primary lesion at injury site: papule, pustule, nodule, abscess, verrucous growth
- Lymphocutaneous sporotrichoid spread: ascending lymphangitis, multiple subcutaneous indolent painless granulomas
- Untreated: Dissemination to gastrointestinal, pulmonary, and central nervous systems; osteomyelitis

Differential Diagnosis
- Atypical mycobacteriosis, nocardiosis, tuberculosis, furunculosis, cat scratch disease, anthrax, tularemia, histoplasmosis, coccidioidomycosis, North American blastomycosis

Diagnosis
- Histologic section stained with periodic acid-Schiff and methenamine-silver: 3 to 5 μm oval and elongated, budding cells ("cigar bodies")
- Tissue culture preparation: diagnostic delicate hyphae and conidial clusters ("rosettes")

Treatment
- Potassium iodide, 2 to 6 grams orally a day until a month after apparent recovery
- Local wound care

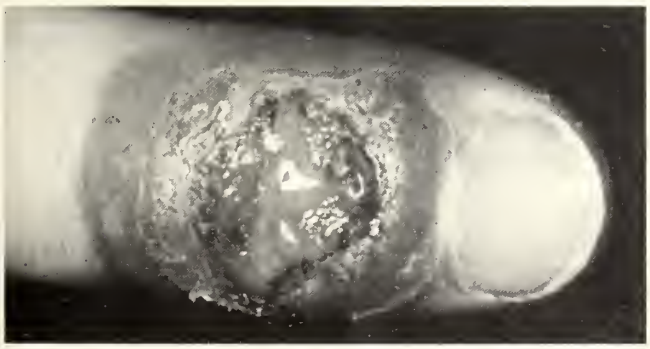

Figure 1.—A primary lesion on the distal radial aspect of the left thumb shows well-demarcated ulcerated plaque with erythematous borders.

Figure 2.—A linear array of erythematous nodules extends proximally from the primary lesion.

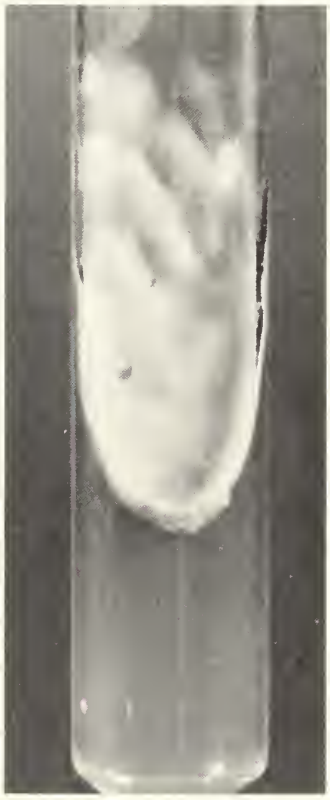

Figure 3.—Mycelial colony growth occurred 5 days after tissue was inoculated on Sabouraud's dextrose agar medium.

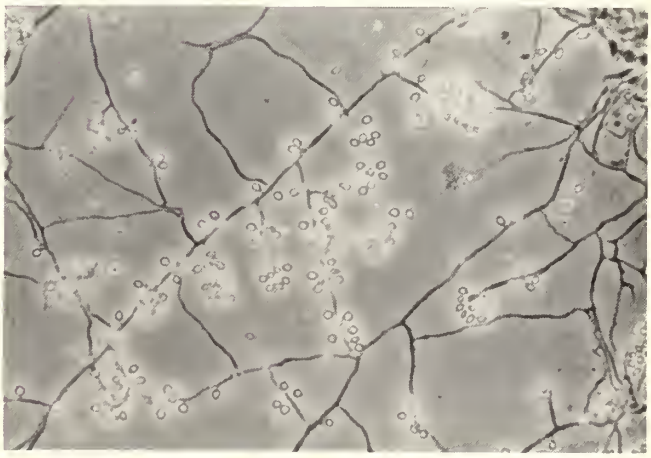

Figure 4.—A photomicrograph of a slide culture using potato dextrose agar shows delicate hyphae and conidial clusters forming "rosettes" diagnostic for *Sporothrix schenckii* (lactophenol cotton blue stain, original magnification × 1,000).

Human sporotrichosis can be categorized as fixed (or localized) cutaneous, lymphocutaneous, primary pulmonary, and disseminated (or systemic) infections. By far the most common presentation is lymphocutaneous spread characterized by a primary ulcerative lesion and nodular extension in a linear fashion along the lymphatic drainage routes—"sporotrichoid" distribution.

Fixed cutaneous infections are less common. This presentation is thought to depend on both host[12] and fungal[13] characteristics. These include the site of infection, age, immunity, and previous sensitization of the host and the thermosensitivity of the infecting organism. Fixed cutaneous infections present as a single lesion or group of lesions without regional involvement.

Primary pulmonary and disseminated infections are both rare and are related in part to a large respiratory inoculum and immunocompromised states,[14] respectively. Classic joint and bone involvement includes the knee, hand, wrist, elbow, and ankle joints and the tibia, respectively. Signs of inflammation are present without associated constitutional symptoms. Roentgenographic clues include osteoporotic and osteolytic areas with periarticular soft tissue swelling. Bony destruction may occur without osteoblastic response.[15]

The incubation period following cutaneous *S schenckii* infection ranges from one to two weeks to several months. The primary lesion ulcerates, and typically painless subcutaneous nodules develop, extending linearly along the area of lymphatic drainage. The nodules may spontaneously drain, and a cordlike structure may be palpated between them. Except in disseminated cases, constitutional symptoms are generally absent. Cellular response is both suppurative and granulomatous.

Left untreated, the infection will generally progress with increased potential for systemic spread, although sporadic reports have described a spontaneous resolution of cutaneous cases.[16] Pulmonary and disseminated infections bear a more ominous prognosis with a potential for the involvement of bone, joints, lungs, muscle, liver, spleen, pancreas, kidneys, testicles, epididymis, breasts, eyes, heart, thyroid, sinuses, and the central nervous system.[17]

The differential diagnosis for lesions revealing sporotrichoid spread includes atypical mycobacterial infections, nocardiosis, tularemia, leishmaniasis, and other fungal infections. Laboratory notification should, therefore, be made to allow for proper isolation procedures.[18]

The diagnosis of sporotrichosis is important because treatment is both unique and narrow in spectrum. Skin testing is not diagnostically helpful, and skin test antigen reactions are often nonspecific. Primary lesion exudates and aspirates are generally nondiagnostic due to either a paucity of organisms or an alteration in the nature of the fungus.[17] Punch biopsy specimens of the primary lesion and associated nodules may reveal characteristic spores, but tissue from deep within the wound easily grows the fungus required for diagnosis.

The organism grows as a cream-colored mold on Sabouraud's medium at room temperature well within three to seven days. The yeast phase grows at 37°C. Authors have promoted this as a simple office procedure,[2] but cultures should be kept for at least a month to prevent false-negative results. The specimen characteristically becomes wrinkled and black with time. Because material for culture may be difficult to obtain in disseminated sporotrichosis, adjuvant serologic and skin tests may be used for diagnosis and treatment monitoring.[17]

The first line of therapy for fixed cutaneous and lymphocutaneous cases is an oral saturated solution of potassium iodide (SSKI). The dose is initiated at 15 drops a day given three times a day. It is gradually increased to a maximum of 120 drops a day as tolerated. Possible adverse reactions include nausea, vomiting, parotid gland swelling, acneiform rash, coryza, and sneezing. With toxicity, the drug therapy should be discontinued for a few days and then restarted at a lower dosage. The treatment course may extend for several months including four weeks of therapy following lesion resolution. Treatment failures are documented with clinical worsening, iodide toxicities, or if no improvement is noted after an adequate trial of maximal therapy.

Until recently, when potassium iodide use was contraindicated or failed, amphotericin B was the alternative drug of choice. Parenteral treatment with amphotericin B involves a total dose of 1.5 to 2.5 grams, and it is associated with a high adverse effect profile. Even then, the use of amphotericin B alone or in conjunction with SSKI and ketoconazole may prove inadequate.[19]

Itraconazole, an orally absorbable triazole derivative, has been clinically proved efficacious for a variety of superficial mycoses and dermatophytoses.[20] Recent reports have shown an excellent curative response for both lymphocutaneous and fixed cutaneous sporotrichosis using itraconazole in a single daily dose of 100 mg for 90 to 180 days. This may represent a second-line regimen, as SSKI is still considered more cost-effective therapy, and amphotericin B use is associated with substantial side effects.[21]

Local heat may be used as adjuvant therapy for cutaneous lesions. In cases where the use of SSKI is suboptimal or contraindicated, thermotherapy may be of great benefit, especially in fixed cutaneous cases.[9] Surgical considerations in extracutaneous cases include debriding osteomyelitic foci, draining synovial fluid, synovectomy, or pulmonary resection.

Affected cats may also be treated with potassium or sodium iodide or amphotericin B, depending on the extent and location of disease. The iodides are considered first-line therapy for cutaneous lesions, but cats are susceptible to iodide toxicosis, which warrants close follow-up. As with human cases, treatment should be continued a month after lesions regress.

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Transmission of Malaria in San Diego County, California

MICHELE M. GINSBERG, MD
San Diego, California

THREE ELEMENTS are required for malaria transmission to occur: the presence of the vector, a susceptible population, and introduction of the parasite. An *Anopheles* species mosquito, the vector, is present throughout California and much of the southern United States. Because there is no immunity to malaria, the population is susceptible. Finally, the parasite has been brought to southern California by seasonal agricultural workers from areas endemic for malaria. Malaria involving migrant workers and local residents has occurred in San Diego County, California, during four of the past five summers.

The first outbreak of malaria in San Diego occurred in 1986.[1] Five migrant farm workers were evaluated in an emergency department over the Fourth of July weekend, diagnosed with malaria, treated, and discharged. Reports reached the San Diego County Department of Health the following week, and the affected persons could not be located for interview. The occurrence of five cases at one time suggested a common exposure. We surmised that the index case was parasitemic early in June, mosquitoes were in contact with that person, and that the five men seen on July 4 were the first wave of subsequent cases. Indeed, a second wave of malaria involving 22 people started late in July. This time, the site of exposure to mosquitoes was identified. Vector control personnel conducted trapping of mosquitoes, larvaciding, and fogging activities. The epidemiologic investigation, including interview and blood examination of exposed persons, permitted the treatment of diagnosed patients and chemoprophylaxis of those having exposure.

Additional episodes of locally transmitted malaria occurred in San Diego during 1988, 1989,[2] and 1990. Features common to these outbreaks include the presence of *Anopheles hermsi* mosquitoes, migrant workers living in the north county area without adequate shelter and protection, and the introduction of the parasite by a migrant worker having malarial parasites in the blood. The lack of ready access to medical care, a reluctance on the part of the migrant worker to seek such care, and the lack of satisfactory housing provide continued opportunities for similar outbreaks to occur.

A key to limiting morbidity related to malaria is the rapid identification of cases and the definition of the geographic area of their exposure. A 24-hour direct telephone reporting of possible malaria cases was instituted during the summer of 1986 and is ongoing. On public health notification of a suspected case, patients are immediately interviewed to determine their exposure history. If the person is a migrant worker living in the fields, a bilingual public health nurse will accompany the patient to the area of residence, initiate an interview of others residing in that area, obtain blood specimens for laboratory examination among those who are symptomatic, and alert vector control personnel to initiate an environmental evaluation of the region. The environmental evaluation includes light traps for mosquitoes, larvae collection, and subsequent treatment of the area. When large populations of *Anopheles* species mosquitoes are identified and individuals who may be harboring the parasite are recognized, chemoprophylaxis with chloroquine phosphate has been used and control measures are applied to reduce and eliminate the mosquito vector. Efforts to contain the problem without dispersing persons who may be parasitemic to other areas have been successful. Public health nurses have gained the trust of the workers, permitting case detection and appropriate treatment.

During the 1986 outbreak, the diagnosis of malaria in a local resident with exposure to infected mosquitoes was delayed. The initial differential diagnosis of this older man with fever and gastrointestinal symptoms did not include malaria because he had not traveled outside of the United States. He had contact with mosquitoes during early evening walks near a lagoon. The diagnosis was established on examination of a peripheral blood smear.

Since 1986, an aggressive program has been established to alert medical practitioners, hospital infection control personnel, and emergency department staff to the potential of locally acquired malaria. Each spring, medical practitioners are sent a bulletin discussing malaria, including its clinical manifestations, diagnostic procedures and treatment, investigative services, and the availability of the public health laboratory and epidemiology services to assist in confirming the diagnosis. Informational sheets are sent to farmers and ranchers in the region, alerting them to the potential of malaria and familiarizing them with symptoms. They are requested to report the presence of large numbers of mosquitoes to vector control personnel.

Migrant encampments have ranged from plastic tarps suspended from trees to plywood shacks. All lack protection from mosquitoes and are within feet of a water supply that sustains mosquito breeding. Public health personnel discuss sanitation and waste disposal and provide education about mosquito-borne diseases. Fliers describing the symptoms of malaria are available in English and Spanish. Persons are urged to call the public health department if symptoms compatible with malaria occur and to seek medical attention immediately.

Excellent cooperation has been obtained from the medical

(Ginsberg MM: Transmission of malaria in San Diego County, California. West J Med 1991 Apr; 154:465-466)

From the County of San Diego Department of Health Services, Division of AIDS and Community Epidemiology, San Diego, California.

Reprint requests to Michele M. Ginsberg, MD, Public Health Services, Division of AIDS and Community Epidemiology, 1700 Pacific Highway, San Diego, CA 92101-2419.

community. A prompt reporting of suspected and diagnosed cases of malaria has permitted immediate interviews, the identification of the area of residence and of exposure, and a prompt assessment of malaria risk to others. Swift action and early diagnosis have reduced the spread of malaria. During 1989 and 1990, no second wave of cases occurred following an initial recognition of malaria transmission. In addition, early diagnosis has reduced the need for hospital admission among those who were infected.

The occurrence of malaria in San Diego and California is not unique. In 1990, local transmission of malaria was recognized in Florida,[3] another area where *Anopheles* species mosquitoes are endemic and free-standing water is available. The pattern of malaria transmission in San Diego County reminds us that the elements necessary to sustain the spread of this and other "manageable" health problems are present. The challenge to medical practitioners is to take a complete history and identify all possible exposures. Laboratories are challenged in examining for parasites and other organisms rarely seen in local residents. Consultation may be obtained from local county and state health departments.

The containment of parasites or bacteria requires maintaining sanitation, personal hygiene, and adequate housing. These outbreaks of malaria remind us that we are at risk for the spread of the disease. Only the maintenance of a sanitary, safe environment and preventive activities can eliminate the effects of this illness in the community.

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Daunorubicin, Amsacrine, and Sinus Arrest

L. ALLEN KINDMAN, MD
JUNE S. ALMENOFF, MD, PhD
VIC A. NARURKAR, MD
Stanford, California

KATHLEEN BLAKE, MD
Albuquerque, New Mexico

CARDIAC RHYTHM and conduction disturbances have been associated with the use of both the anthracycline antibiotics doxorubicin (Adriamycin) and daunorubicin and the aminoacridine amsacrine. They have been noted with routine clinical use in humans and under experimental conditions in animals. These disturbances have consisted of atrial fibrillation and atrial flutter, sinus bradycardia and sinus tachycardia, ventricular premature contractions, and ventricular tachycardia, in addition to the loss of voltage on the surface electrocardiogram (ECG), the appearance of fascicular blocks, and nonspecific and ischemic changes in the ST segment. First- and second-degree heart block have been reported clinically with the use of doxorubicin but not with that of amsacrine.[1,2] Atrioventricular dissociation has been described in at least three cases involving the use of daunorubicin.[3,4] While these rhythm disturbances are usually asymptomatic, there have been reports of sudden death temporally associated with the administration of either class of agents and thought to have been caused by ventricular tachycardia or ventricular fibrillation.[2,5,6] Sinus arrest has not been described with either class of agent. We report the case of a patient with acute myelogenous leukemia in whom the administration of these agents was temporally associated with the appearance of sinus arrest accompanied by a junctional escape rhythm. Furthermore, amsacrine therapy was also associated with brief episodes of ventricular asystole.

(Kindman LA, Almenoff JS, Narurkar VA, Blake K: Daunorubicin, amsacrine, and sinus arrest. West J Med 1991 Apr; 154:466-467)

From the Cardiology Division and Department of Medicine, Stanford University School of Medicine, Stanford, California. Dr Blake is currently with The New Mexico Heart Clinic, Albuquerque.

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Reprint requests to L. Allen Kindman, MD, Division of Cardiovascular Medicine, Falk Cardiovascular Research Center, Stanford University School of Medicine, Stanford, CA 94305.

Report of a Case

The patient, a 42-year-old Vietnamese man, was diagnosed with acute myelogenous leukemia in May 1987.* He presented with constitutional symptoms, leukemia cutis, and a leukocyte count of 203×10^9 per liter. Before this, he was in excellent health, having a history of borderline hypertension controlled by diet alone but no other cardiac risk factors. Remission was successfully induced with a regimen of daunorubicin hydrochloride, 60 mg per m^2; cytarabine (formerly cytosine arabinoside), 18 grams per m^2; and 6-thioguanine, 18 mg per m^2. Four months later, he was readmitted with a relapse of his disease in the skin, sclerae, and meninges. A routine admission ECG revealed normal sinus rhythm, a rate of 84 per minute with a PR interval of 0.16 seconds, a QRS duration of 0.04 seconds, and a corrected QT interval of 0.41 seconds. The QRS axis was 4 degrees, and there was a nonspecific T wave abnormality in lead F. Salvage chemotherapy consisting of etoposide (VP-16-123), 100 mg per m^2 daily for five days, and cytarabine, 3 grams per m^2 daily for five days, was administered. In addition, intrathecal methotrexate therapy was initiated. The treatment was well tolerated, aside from persistent nausea managed with the intravenous administration of the antiemetics droperidol, 1 to 2 mg every six hours; diphenhydramine hydrochloride, 25 to 50 mg every four to six hours; lorazepam, 1 to 2 mg every six hours; and metoclopramide hydrochloride, 50 mg every six hours. Concomitant therapy included the antibiotics mezlocillin, gentamicin sulfate, and cefazolin sodium for the empiric treatment of fever while he was neutropenic. Because of a poor response to therapy, daunorubicin, 55 mg per m^2, was given over two hours following premedication with the above antiemetics. Daily infusions of both cytarabine and etoposide were continued. Six hours after completion of the daunorubicin infusion, the patient's blood pressure was 80/50 mm of mercury and the heart rate 50 beats per minute, both decreased from their baseline values of 110/70 mm of mercury and 90 to 110, respectively.

An ECG showed sinus arrest with a junctional escape rate of 50 and retrograde atrial activity. Occasional sinus com-

*Stanley Sehrier assisted in the care of this patient and provided helpful comments.

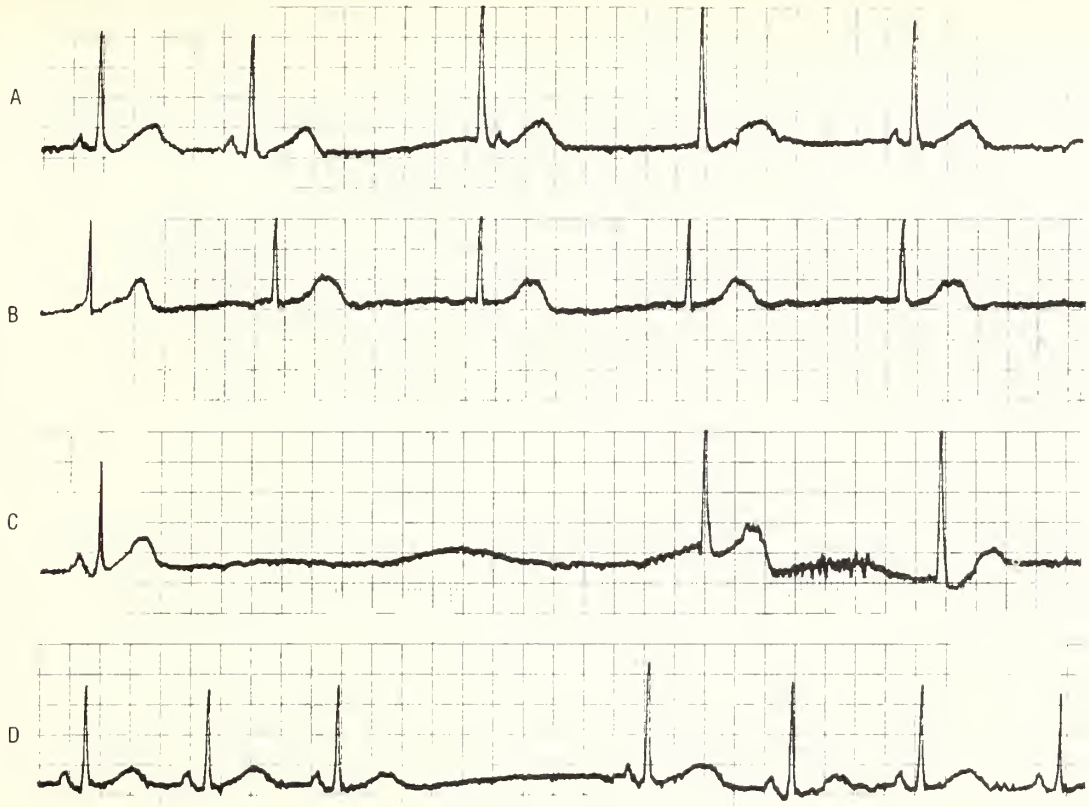

Figure 1.—Representative electrocardiographic tracings show the abnormalities described in the text: **A,** Sinus arrest followed an infusion of daunorubicin hydrochloride. **B,** Junctional rhythm followed the first dose of amsacrine. **C** and **D** are continuous. Sinus arrest and ventricular asystole followed the second dose of amsacrine.

plexes were observed (Figure 1-A). There was no response to the administration of atropine sulfate, 2 mg. At this time, the patient's serum calcium, potassium, and magnesium levels were 2.12 mmol per liter (8.5 mg per dl), 4.4 mmol per liter, and 1.4 mmol per liter, respectively. An echocardiogram showed normal ventricular contractility and borderline left atrial enlargement. The patient was placed on continuous cardiac monitoring with a transcutaneous pacing system at the bedside. Twelve hours after sinus rhythm was restored, amsacrine, 125 mg per m^2, was substituted for daunorubicin and was infused over two hours. Two hours after completion of the infusion, several brief episodes of junctional rhythm were noted on the monitor (Figure 1-B). The patient remained asymptomatic, with a blood pressure of 110/60 mm of mercury. No further arrhythmias were noted for the next 20 hours. A second dose of amsacrine, 125 mg per m^2, was administered. An hour later, sinus arrest with a junctional escape rhythm rate of 50 per minute was noted on the monitor, accompanied by several brief episodes of ventricular asystole, of which the longest was four seconds in duration (Figure 1-C and -D). By six hours, sinus rhythm had returned, and no further episodes of sinus arrest or asystole were noted. At this time, serum potassium and calcium values were 4.5 mmol per liter and 2.05 mmol per liter (8.2 mg per dl), respectively.

The patient continued to receive the aforementioned antibiotic and antiemetic therapy for the next five days, without cardiovascular side effects. Further anthracycline or aminoacridine therapy was withheld because of the poor clinical response. Remission was not achieved, and the patient died of septic complications two weeks later. During this follow-up period, no further episodes of sinus arrest or ventricular asystole were noted. Sinus tachycardia as rapid as 140 beats per minute and considered appropriate to his clinical state was noted. Permission for an autopsy was not granted.

Comment

Amsacrine is known to be cardiotoxic, but its use is generally thought to be associated with fewer cardiovascular side effects than that of the anthracyclines. While various atrial arrhythmias have been attributed to the toxic effects of both classes of drug, this is the first reported instance of sinus arrest. This case shows that both types of agents may cause sinus node dysfunction. In addition, ventricular asystole accompanied the sinus arrest that followed the amsacrine infusion. Sudden death in patients undergoing antineoplastic therapy with anthracyclines and with amsacrine has been ascribed to the occurrence of ventricular tachycardia. These observations suggest that asystole may be an additional mechanism of sudden death in patients undergoing treatment with these agents.

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Editorials

A Time to Lead, a Time to Follow

PHYSICIANS ARE A VITAL PART OF SOCIETY. We are reminded of this daily and especially when "the system" does not seem to be working well. Not long ago, I talked with a worker from a small lead battery plant. He and his family no longer had health insurance. His financially strapped employer had stopped buying the insurance and, instead, had given him a $100 a month raise. "I can't get insurance for my family and me for $100 a month. Anyway, I pay taxes on it, so it isn't even $100. When my toe got infected, I couldn't see a doctor and it was real bad, so I was out of work. The kids haven't gotten their shots. We've got no hope of seeing a dentist." Society hasn't risen to the occasion, at least for that worker.

Society has subsidized our education, whether in public or private medical schools. Society supports the research that underpins our methods, procedures, and prescriptions. Society recognizes our skills by seeking our help at crucial times. As we see the challenges all around, we know that we are among those who must respond most thoughtfully. What more can we do about improving health and access to good health care?

Ralph Crawshaw, our assistant editor for Health and Public Policy and Project Director for Oregon Health Decisions, observes that physicians should be wise civic participants, not just clinicians. Practicing our profession is not enough. Physicians need to engage in active dialogue with patients and policy makers. We need to communicate beyond the chief complaint and differential diagnosis.

We also need to agree about important elements in any new health care proposal. These elements include basic care for all; prevention of disease and disability; physician accountability; ease of access, ease of payments; integration with social, nutrition, and housing services; more emphasis on the system's function than structure; a certain tempering of patients' expectations regarding diagnosis, treatment, and cure, which could lead to decreased physician liability. In addition to meeting all of these criteria, patients and physicians must feel good about the proposed system. This satisfaction makes sharing responsibilities more of a partnership than a burden. There is, as we are all taught, a physician/patient relationship. Who is the leader? Who is the follower?

In his recent book, *On Leadership,*[1] John W. Gardner, philosopher-statesman and former Secretary of the Department of Health, Education, and Welfare, describes his and others' views on leadership. In doing so, he also focuses on "followership." He notes, "Followers do like being treated with consideration, do like to have their say, do like a chance to exercise their own initiative—and participation does increase acceptance of decisions." He describes early sociologist Georg Simmel's theories by saying, "In a sense, leadership is conferred by followers." Gardner's practical answer to a query on leadership: "The most important thing to have in mind is that leaders need followers." Finally, "In the conventional mode people want to know whether the followers believe in the leader; a more searching question is whether the leader believes in the followers."

If physicians are to help lead in designing and implementing solutions to America's health care challenges, we must listen carefully to our patients. We must recognize and work toward meeting their needs. We must have their trust. Indeed, in some respects we must be their followers.

The physician/patient relationship goes far beyond office walls. It is far grander than one to one. It extends across the country and throughout all segments of society. It is a partnership of leaders and followers who need to respect one another and to communicate well. We should do everything we can to learn from and support one another; to lead, to follow.

LINDA HAWES CLEVER, MD

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Women Mentors Needed in Academic Medicine

WOMEN IN MEDICINE and other fields are increasingly filling positions at the lower levels of the academic ladder, but relatively few can be found at the ranks of associate and full professor. The explanation sometimes given is that there is an insufficient number of more senior women. This explanation might have been true when the number of women entering medicine was just starting to increase. After two decades in which substantial numbers of women have entered medicine, however, it cannot account for the failure in recent years to show increases of women in tenured positions. It is difficult to explain why there has been no increase from 1985 to 1989 in the proportion of female associate professors in medical schools (20% at both times). It is even more difficult to explain why, during this time the proportion of female full professors on medical faculties actually dropped from 10% to 9%.[1]

In this issue, Levinson and colleagues point to one reason why women may have difficulty ascending the academic ladder[2]: the lack of mentors and role models. Their study does not address this lack directly. Rather, it demonstrates the contribution to achievement for women in academic medicine of having mentors and role models. If having mentors and role models facilitates achievement and if women have less access to mentors and role models than do men, it will be more difficult for women to succeed.

Several studies in addition to the one in this issue have shown the beneficial effects of mentoring on career success.[3,4] Of a sample of almost exclusively male senior faculty surveyed at one medical school, 90% reported that they had had a mentor and that this had assisted them in their career development.[3] In a sample of female lawyers, those who had a true mentor—meeting precise criteria for the types of support that a mentor gives—showed greater career success and satisfaction than did women who had no mentor. They were also more successful than the women who reported that they had had a mentor but for whom the actual mentoring activity did not meet the criteria. Moreover, the women who did not have a true mentor but pieced together support from different people were not as successful and satisfied as those who had had a single mentor.[4]

Compared with male physicians, female physicians in an academic community appear less likely to have the benefit of a mentor. In a recent (1990) study of medical students, house staff, and junior faculty at one medical school, twice as many female than male house staff and junior faculty reported that

they had never had a mentor.[5] In the sample studied by Levinson and co-workers, minority women were even less likely than their white female colleagues to have the benefit of a mentor.

Because a mentor could be either male or female, the small number of women in senior positions who could serve as mentors theoretically does not preclude more junior women from obtaining mentoring. In truth, the scarcity of high-level academic women as mentors is problematic. First, male faculty may be less likely to develop a mentoring relationship with a female student or junior faculty member than with a male. One motivation for senior faculty of developing a mentoring relationship may be the sense of reproducing oneself. In selecting a protégé, faculty members may, without their own awareness, lean towards selecting persons who are of the same sex and race. The bias toward selecting a protégé who is similar to oneself (beyond a similarity in area of academic interest) works against women and minorities.[6] Further, insofar as male faculty may think that women will be less likely to succeed in academic careers, they may shy away from taking them on as protégés. This can become a self-fulfilling prophecy if women then do not have access to the information and help that a mentor can provide.

These processes are subtle. As Menges and Exum note in reviewing barriers to the advancement of women and minority faculty in academia, "slow progress is less the result of deliberately prejudiced actions than the failure of persons of good will to ensure equity."[7(p139)] Even if the selection of protégés were equal by sex, there would still be a problem for women who had male mentors. While either a man or woman can be a mentor for a woman, only a woman can fully constitute a role model for another woman. As Levinson and associates note, while mentors provide guidance on professional issues, role models provide an example of both professional and personal life.[2] For most women, the example of other women successfully combining a satisfying personal and professional life provides critical information and motivation to aspire to a similar role.

In their study, Levinson and co-workers found a more powerful effect of having a mentor than of having a role model in terms of career success, although both were related to career satisfaction. This finding should be interpreted cautiously. First, as the authors note, the survey was of full-time faculty. A lack of role models may play a particularly strong role in the decision of women not to continue in academic medicine. In addition, the analysis compared women who reported having an ongoing relationship with a role model with those who did not.[2] Effective functioning of role models may or may not require an ongoing relationship. It may be that among those women who reported not having had an ongoing relationship with a role model were women who had previously had a role model who provided them with a positive image of the possibilities of an academic career in medicine. If this is combined with currently having a mentor, a woman may have both the motivation and the practical support necessary to persevere and succeed. In future research, it would be useful to examine the joint and separate functioning of role models and mentors and to consider the question of the nature and timing of influence of each.

Levinson and colleagues discuss possible remedies to the lack of role models and mentors for women in academic medicine.[2] These include encouragement for senior faculty to place a high priority on providing mentoring and encouraging junior women to seek out such relationships and to develop other resources, including peers, to supplement lacks in the mentoring they may receive. Unfortunately, there is reason to think that these measures will fall short of achieving the kind of change that is necessary to improve substantially the situation for women in academic medicine. The processes noted earlier may be subtle but they are nonetheless powerful. It is not enough to encourage senior faculty to mentor. There are already too many good and worthy activities that faculty "should" engage in. True incentives for such activity are needed, including considering mentoring activity as a critical aspect of merit and advancement for senior faculty. In addition, incentives are needed to help junior faculty who might not otherwise be selected as protégés. Further, there is no substitute for having a sufficient number of women in senior positions to serve as role models. To accomplish this, institutional changes are needed that enable and encourage women to stay in academic careers. This involves some change in the academic climate, which has been a "chilly" one for women.[8] Policy changes are needed to make it easier for women as well as men to combine family and career. Recent policies adopted by some medical schools to establish childbearing and family care leave, including procedures for slowing the tenure clock, are examples of policies that will help to keep women in the academic track.

Felice Schwartz has argued in the *Harvard Business Review* that women were moving into a seller's market in the corporate world ("Management Women and the New Facts of Life," January-February 1989, pp 67-76). This change was occurring because institutions were recognizing that "80% of new entrants in the work force over the next decade will be women, minorities, and immigrants" (p 68). These demographics will affect medicine as well. To get the best physicians to teach, do research, and care for patients, medical schools will need to recognize the need for women and the needs of women.

NANCY E. ADLER, PhD
Professor of Psychology
Departments of Psychiatry and Pediatrics
University of California, San Francisco, School of Medicine

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Hypoglycemia—A Major Risk of Insulin Therapy

IN THIS ISSUE of the journal, Dr Service describes the pathophysiology, evaluation, and treatment of hypoglycemia.[1] I will focus on one of the most common causes of hypoglycemia: iatrogenic hypoglycemia secondary to insulin treatment of diabetes.

How common is hypoglycemia? Most experienced clini-

cians recognize that minor hypoglycemic reactions are extremely common in patients with insulin-treated diabetes mellitus.[2] In the randomized Diabetes Control and Complications Trial (DCCT), hypoglycemia occurred approximately once per week in the standard treatment group and approximately twice per week in the intensive treatment group.[3] Less well recognized is that severe hypoglycemia, defined as coma, seizure, a reaction requiring admission to a hospital, or intravenous glucose or glucagon therapy, are also common.[2] Basdevant and co-workers reported that during a one-year period of observation, 17% of patients had a severe hypoglycemic reaction.[4] Similarly, in the DCCT study 9.8% of subjects in the standard treatment group had severe hypoglycemia during the 12 months of study.[3] Not all studies have shown this high a frequency of severe hypoglycemia, which may be due to differences in patient populations, education of the patients, the goals of therapy, treatment regimens, or the degree of normalization of glucose levels.

Is hypoglycemia a serious side effect? Deaths due to hypoglycemia are a surprisingly frequent iatrogenic complication.[2] For example, 2.8% of insulin-dependent diabetic patients treated at the Joslin Diabetes Center (Boston, Mass) died of hypoglycemia. In other studies, between 2% and 7% of deaths in insulin-dependent diabetics were caused by hypoglycemia.[2] Brain damage due to insulin-induced hypoglycemia has unfortunately been observed by most experienced diabetologists, but the incidence of brain injury has not been carefully investigated. Whether hypoglycemia causes subtle long-term neurologic sequelae has not been definitively proved, but there is considerable evidence suggesting that hypoglycemia may have harmful consequences.[2] In a study by Golden and associates, a high frequency of hypoglycemia was associated with decreased abstract-visual reasoning.[5] The frequency of insulin-induced hypoglycemia causing motor vehicle accidents or other accidental injuries is unclear.[6] In a small survey of 250 insulin-dependent diabetic patients, 13 (5.2%) admitted that hypoglycemia had caused a motor vehicle accident.[7] Finally, the role of hypoglycemia in causing rebound hyperglycemia (Somogyi effect) continues to be debated with both positive and negative studies.[8,9]

Which diabetic patients are likely to have serious hypoglycemia? A number of medical conditions such as pituitary or adrenal insufficiency, end-stage liver or kidney disease, ethanol abuse, therapy with β-blockers, and psychiatric disturbances have been recognized to predispose to serious hypoglycemia.[2] Furthermore, as discussed by Service, there is a counterregulatory hormonal response to hypoglycemia, primarily involving the secretion of glucagon and epinephrine, that produces an increase in serum glucose levels and protects from hypoglycemia.[1] In persons with diabetes, this counterregulatory hormonal response is frequently impaired.[2] Patients with diabetes for several years have a reduced glucagon but normal epinephrine response to hypoglycemia resulting in a modest delay in glucose recovery. After a longer duration of diabetes, both the glucagon and epinephrine response are deficient, resulting in a marked impairment in recovery from hypoglycemia. In some studies a delayed or absent rise in glucose levels after experimentally induced hypoglycemia has predicted an increased risk of severe hypoglycemia with aggressive insulin therapy.[10]

Does tight glucose control increase the risk of hypoglycemia? In the DCCT study, subjects in the intensive treatment group had a threefold increase in the incidence of serious hypoglycemia compared with those in the standard treatment group (intensive treatment 26% versus standard treatment 9.8%, $P < .001$).[3] Others have also noted an increased risk of hypoglycemia in patients with rigidly controlled diabetes. In addition, studies have shown that patients with severe hypoglycemia are more likely to have decreased hemoglobin A1 levels.[11] One obvious explanation for these findings is that given the imperfect techniques of glucose control, the closer a person gets to normal glucose levels the less margin of error there is, and the more likely one is to overshoot and induce serious hypoglycemia. In addition, studies have shown that the body's homeostatic response to hypoglycemia is reduced by tight glycemic control.[12-14] The glycemic threshold for the release of counterregulatory hormones is lowered by improved glycemic control, resulting in an impairment in the recovery from hypoglycemia. Furthermore, because the adrenergic symptoms of hypoglycemia—anxiety, cold sweats, tachycardia, hunger—are caused by epinephrine secretion,[2] the early recognition of hypoglycemia is also impaired in patients with well-controlled diabetes.[14] Consistent with this observation are reports that following the initiation of intensive insulin therapy, the recognition of hypoglycemia is impaired.[15] Of great importance is that while the threshold for counterregulatory hormone release is decreased, the glycemic threshold for impairment in cognitive function is not altered by strict glycemic control.[16] Thus, tight glycemic control in addition to reducing the margin for error also induces alterations in counterregulatory hormone response that are likely to increase the risk of severe hypoglycemia.

How can serious hypoglycemia be prevented? All patients with diabetes need to be educated regarding the possible dangers of hypoglycemia. Patients need to be instructed as to the symptoms of hypoglycemia and what actions they should take if hypoglycemia occurs. Particularly important, and often overlooked, is the measurement of blood glucose levels to confirm the presence of hypoglycemia.[2] At times patients can have symptoms consistent with hypoglycemia without having low blood glucose levels.[2] In normal persons and diabetic subjects, decreases in blood glucose levels within the normal range can stimulate the adrenergic system and result in symptoms identical to those observed with hypoglycemia.[2] Alterations in therapy based solely on symptoms can lead to unnecessary and counterproductive changes. Patients on insulin therapy should always carry glucose and be strongly encouraged to wear a medical alert bracelet. Family members and close friends should be educated as to the symptoms and signs of and appropriate therapy for hypoglycemia. In persons who have had severe hypoglycemic episodes, instructing family members or close friends in the administration of glucagon can be life saving.

The potential for serious hypoglycemia should not be used as a blanket excuse to avoid improving metabolic control. Rather, one needs to balance the risk of serious hypoglycemia with the possible benefits of improved glycemic control.[2] In patients with a high risk of hypoglycemia, tight control may not be justified. A previous history of severe hypoglycemic episodes is a relative contraindication to strict glycemic control.[3] In addition, in some patients the possible dangers of hypoglycemia may be more serious—history of cardiac or cerebrovascular disease, living alone, and the like—and therefore tight glycemic control may not be indicated. Furthermore, there are patients, such as those with severe preexisting diabetic complications or a decreased life

expectancy from other medical conditions, who are unlikely to benefit from tight metabolic control, and in these patients the risk of hypoglycemia occurring outweighs the potential benefits. It is essential that physicians weigh the benefits and risks and tailor a therapeutic regimen to the needs of individual patients.

KENNETH R. FEINGOLD, MD
Department of Medicine
University of California, San Francisco
Metabolism Section
Veterans Administration Medical Center
San Francisco, California

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An Agenda for Public Health in the 1990s

THESE ARE EXCITING and dynamic times in public health, preventive medicine, and health care in general. Profound changes are underway in health care services delivery. We have entered a new era of consciousness and concern about the healthfulness of the food we eat, the water we drink, the air we breathe, and the overall global environment. There are new and frightening problems before us such as AIDS and drug abuse, while long-recognized health problems such as injury control and inadequate prenatal and children's care continue to cry out for attention. And new health care technology and scientific advances in genetic engineering and other fields are presenting unprecedented moral and ethical dilemmas.

It seems as though there has never been a time when there were more challenges for public health and more opportunities for public health personnel to unite with medical practitioners and other human service professionals. While the list of issues and problems for public health to focus on is long, I think much of the public health agenda of the coming decade will focus on five particular areas.

The first of these problem areas is substance abuse. I would agree with those who have called drug abuse today's number one public health problem in California—and probably in the United States. Drug abuse is tearing apart the very fabric of society in many communities and is causing a skyrocketing increase in illness and death. Examples of this are the following:

- Surveys done by the California Department of Health Services in 1988 revealed that 20% of newborns admitted to neonatal intensive care units in California that year had problems related to maternal drug abuse. The estimated cost for the initial hospital care only of those more than 8,000 infants was more than $40 million. Indications are that this situation has not improved.
- The incidence of congenital syphilis has increased about 500% in the past five years, most of which can be related to the use of cocaine.
- The major cause of new cases of AIDS in many parts of the country, and increasingly so in California, is drug abuse. This disproportionately affects minority ethnic groups. New AIDS cases related to drug abuse are five times more common in African Americans than among other ethnic groups in California.

There are other statistics that could be cited; suffice it to say that drug abuse is causing protean untoward public health effects.

While most of the attention in recent years has focused on cocaine, heroin, and methamphetamines, we should not forget that the first drug of abuse and the first drug of addiction for our children is tobacco. We now know that tobacco is every bit as addictive as heroin or cocaine, and we should view tobacco for what it is—legalized dope. Tobacco use kills more than 40,000 Californians every year—far more than that of cocaine or heroin—and it costs California more than $25 million a day in medical expenses and lost productivity.

If we are going to wage a war on drugs, we need to begin with a war on tobacco. I am pleased that we have initiated one in California.

The second major public health challenge of the 1990s—for both California and the rest of America—is assuring the availability of access to basic health care for all of our citizens. It is ironic that whereas many Americans receive the most technologically advanced and the best medical care available any place in the world, a large and growing number of our citizens go unattended, having no or inadequate access to even the most basic health care services. This paradox of medical need amidst medical plenty has developed over many years as a result of complex and powerful forces that cannot be easily changed. But change must occur!

As a society, we should set a goal that by the end of this decade, if not sooner, *all* Americans should be guaranteed access to at least basic health care.

A third area of particular concern for public health in the 1990s will be genetics and genetic-related diseases. Genetic engineering and techniques such as in vitro fertilization and chorionic villus sampling, as well as other new and rapidly developing technologies, will have a major effect on public

health and health care in the future. For example, DNA screening for the probability of heart disease, certain cancers, muscular dystrophy, or cystic fibrosis developing is nearing potential wide-scale application. The effect of these new technologies on traditional public health programs will be profound. This whole area is about to bloom.

A fourth major public health challenge of the 1990s has to do with our burgeoning population, of California, the United States, and, most important, of our planet. In many places in the world today, unchecked population growth is surpassing the ability to provide for even the most basic human needs. Closer to home, gridlock on the freeways, increasing social violence, and crowded classrooms are but some of the manifestations of the difficulty we are having dealing with population growth, even in a place as affluent as California.

The increasing struggle to meet basic human needs with an ever shorter supply of natural resources intensifies the threat of local, regional, or even global armed conflict. When these conditions are combined with 24-hour-a-day electronic media coverage of terrorist attacks, political coups, and mass murders that further depersonalize human beings and serve to normalize interpersonal violence, there is clear reason for concern.

Also of increasing concern is the potential for continued unchecked population growth to present some unique public health problems. For example, there is likely to be increased vulnerability of the human population to epidemic diseases as the number of people increases, as crowding becomes more severe, as environmental conditions deteriorate, and as malnutrition and the resultant population immunocompromise worsen. These conditions combined with high-speed transportation and an ever more cosmopolitan world provide the conditions favorable for the rapid spread of ancient and novel plagues.

The fifth major public health challenge of the 1990s is the problem of ecosystem health. Every day we are made more aware of problems related to the earth's stressed ecosystem. Global warming, stratospheric ozone destruction, marine pollution, acid rain, and massive tropical deforestation all attest to a deteriorating global environment. In the past decade, we have learned how difficult and expensive it is to remediate environmental transgressions once committed. While there is much yet to learn about both preventing and remedying these problems, they need to be vigorously addressed now.

Yes, we have many complex and tough public health and health care problems to deal with in the 1990s—problems that go to the roots and fabric of our chemical-intensive, electronic-driven, sophisticated late-20th-century society. They are problems that we have created and that we can still fix.

If we were pessimistic, we might see nothing but problems because the challenges seem to be so great. By the same token, though, the opportunities are great. We could approach these problems pessimistically, seeing only the difficulties, or we can approach them optimistically, seeing opportunities within the difficulties. It's our choice. It's our world. We have to ask ourselves what kind of future we want, and then we have to go out and create it.

Adapted from a speech given at a commencement of the UCLA School of Public Health, June 16, 1990, Los Angeles, California.

KENNETH W. KIZER, MD, MPH
Director
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MEDICAL DIRECTOR. Family Practice Physician (BC/BE) for community based clinic. Emphasis Family Planning, Primary Care, Pediatrics, STD and health education. Responsibile for medical policy, QA, and supervision of clinical staff. Bilingual/cultural Hispanic preferred. Inquiries to EVCC, 2470 Alvin Ave, #3, San Jose, CA 95121. EOE.

SEATTLE, Washington suburban 26 physician primary care group has immediate need for Family Physicians and Internists. Area growth has created the need for a team physician who enjoys work as well as play in the beautiful (and affordable) Pacific northwest. Remuneration includes salary, bonus, and fringe benefit package. For more information, please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

GENERAL INTERNIST IN THE PACIFIC NORTHWEST. Busy 30 doctor multispecialty group practice looking for General Internist with ICU skills and interests to join an existing Internal Medicine department. Competitive salary and benefits; ownership status available after 18 months of employment. Send CV to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

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(Continued on Page 477)

(Continued from Page 476)

PEDIATRICIAN. Well established busy solo-practice available in suburban Seattle area. Excellent location adjacent to modern hospital. Level II newborn nursery. Ideally suited for Pediatrician with some experience who likes independence. Building may be purchased at later date. Present Pediatrician to retire this fall. Will introduce. Inquiries to Evergreen Pediatrics, 12819 120th Ave NE, Kirkland, WA 98034.

CALIFORNIA. Immediate permanent placement opportunities in General Internal Medicine, Plastic Surgery, Urgent Care, OB/GYN, Pediatrics, Orthopedics, Otolaryngology, Family Practice, and Dermatology. For information call/send CV to Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762, fax (415) 376-0813.

MULTISPECIALTY MEDICAL CLINIC seeking Family Practice or Emergency Room Physician for their fast-paced Urgent Care department. 13 to 15 six-hour shifts per month with expansion of hours with the completion of a satellite facility. Board certified. Partnership track. Contact Jeanette Applegate at the Santa Cruz Medical Clinic, 2025 Soquel Ave, Santa Cruz, CA 95062; (408) 458-5592.

SAN JOAQUIN VALLEY. Excellent opportunity for Family Practitioner to serve the underserved. No night call or weekends. Competitive salary plus benefits, paid malpractice. Agricultural community, one hour from the mountains, two hours from the coast. Bilingual English-Spanish helpful. Send CV to Hugh F. Stallworth, MD, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

BC/BE RADIOLOGIST. Exceptional northern California location. Diagnostic and interventional fee-for-service practice. All imaging modalities represented. Academic appointment available. Comfortable workload; excellent quality of life. Contact Carol Westfall, Cejka & Company, 222 S. Central Ave, Ste 700, St. Louis, MO 63105; phone 1 (800) 765-3055.

CARDIOLOGY. Invasive Cardiologist join noninvasive; new Cath lab; north bay area. Huge opportunity. Electrophysiologist even better. Résumé to Number 234, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602. ASAP.

ESTHETIC SURGERY—SOUTHERN CALIFORNIA. BC General Plastic Surgeon to associate with ENT. Practice 99% cosmetic. Desire emphasis in breast/body contouring to complement current practice. Send CV to PO Box 3421, Santa Barbara, CA 93120.

BC/BE PULMONARY/CRITICAL CARE—SAN FRANCISCO BAY AREA. Physician sought to join two busy Pulmonologists in Marin county, 10 miles north of San Francisco. Excellent opportunity to be part of a well established practice, which would include inpatient and outpatient consultation and active involvement in the Intensive and Coronary Units at a superb community hospital. Guaranteed salary and benefits are available now but we will be willing to wait for completion of training in 1991. Send CV to Alan Margolin, MD, 900 S. Eliseo Dr, Greenbrae, CA 94904.

SPOKANE, WASHINGTON. Primary Care Physicians join with Annashae Corporation in providing patient care to the families of the men and women serving in the Armed Forces. Immediate Emergency Room positions available in Spokane, Washington. Weekends and holidays. Competitive remuneration. Malpractice covered. Licensure any state. ACLS required. Contact in confidence Annashae Corporation, 230 Alpha Park, Cleveland, OH 44143-2202; 1 (800) 245-2662, EEC/MF.

PATHOLOGIST, BC/BE—CENTRAL CALIFORNIA VALLEY. Seven member group seeks associate for independent multiple hospital and private laboratory practice. Send CV to Robert F. Chard, MD, Delta Pathology Associates Medical Group, 2291 W. March Ln, Ste 179E, Stockton, CA 95207.

(Continued on Page 478)

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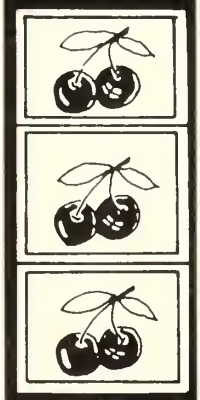

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PHYSICIANS WANTED

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

JUNIOR FACULTY INTERNIST. University of California, San Francisco, Valley Medical Center, Fresno Medical Education Program, Department of Family Practice seeks recent BE Internal Medicine graduate to attend on a general Internal Medicine ward, teach in the ambulatory setting and contribute to the intellectual life of the Department. Our full-time experienced Senior Internist will provide faculty development, consultation, and backup. VMC is a major affiliate of UCSF School of Medicine sponsoring several well regarded programs, including Internal Medicine. Delightful and affordable central California location. Salary guarantee and faculty practice plan incentive. Available July 1, 1991. Send CV to Robert Heiligman, MD, Assistant Chief of Family Practice, 2212 N. Winery, #130, Fresno, CA 93703. EOE, women and minorities are encouraged to apply.

INTERNAL MEDICINE PHYSICIAN (BC/BE) sought to join distinguished group of five others in a highly respected and successful practice situation in large east San Francisco bay city. The group owns its own modern building located in the heart of the medical community and within walking distance of two excellent hospitals. Excellent financial arrangements and benefits. Clinical faculty appointment with UCSF possible. For full details contact Mr Clifford Carpenter, (415) 834-7559, fax (415) 451-5517. CVs to 245 Lee St, Ste 109, Oakland, CA 94610.

MEDICAL DIRECTOR: HIV Clinic of Marin County, California. Full-time position approximately June, 1991 for MD with interest and experience in HIV Primary Care. Salary commensurate with experience, plus benefits. BC/BE, Family Practice, Internal Medicine. Send CV/résumé to Louise Fuller, AIDS Program, Department of Health and Human Services, 18 Professional Center Parkway, San Rafael, CA 94904; for information: (415) 499-6722.

FAMILY PRACTICE RESIDENCY FACULTY POSITION—CASPER, WYOMING. University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, BC Pediatrician to be the Pediatric Coordinator of an 8-8-8 Family Practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming. The University of Wyoming is an affirmative action/EOE. Contact Dr David Driggers, Director, University of Wyoming Family Practice Residency, 1522 E. "A" St, Casper, WY 82601; (307) 266-3076.

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Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, Walnut Center, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

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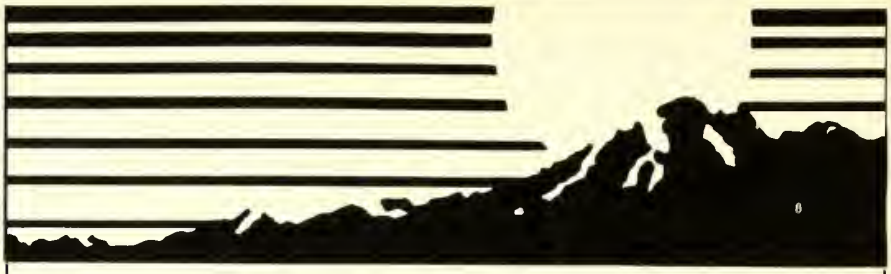

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DENVER, COLORADO – A young, boarded Pediatrician practicing near our 200-bed hospital in the Denver suburbs for the past two years is now seeking an associate.

LAYTON, UTAH – A multi-speciality group here is seeking to add their third Pediatrician. Also, a three-physician group, with two offices, is in need of another member. Layton is 20 miles north of Salt Lake City and 15 miles south of Ogden.

For more information send CV to: Gordon Crawford, Manager, Professional Relations, Humana Inc., Dept. HH-4, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

FAMILY PRACTICE. We operate six Community Health Centers in central California. We have an opening at our new 7,000 square foot facility in Wofford Heights, located one hour east of Bakersfield in a beautiful mountain lakeside resort area. Full lab and x-ray services. Excellent salary and benefit package. Malpractice paid. This is a rare opportunity to combine a very attractive life-style and an excellent practice opportunity. Call George Johnston at (805) 845-3731 for details.

GERIATRICS FACULTY POSITION. The University of California, Davis, School of Medicine is recruiting for a full-time faculty position at the Assistant/Associate/Professor level to assist in an expanding Geriatric Program at UCD. The school has a major commitment to Geriatric Medicine and has already established a Center for Aging and Health. The candidate must be BC/BE in Internal Medicine with appropriate experience in an academic Geriatric/Gerontology program and must qualify for California licensure. A letter outlining research, teaching interests, Geriatric experience and a CV must be received by May 31, 1991. Send reply to John A. Robbins, MD, Internal Medicine, 2221 Stockton Blvd, Room 3107, Sacramento, CA 95817. The University of California is an Affirmative Action Equal Opportunity Employer.

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OB/GYN—SOUTHERN CALIFORNIA. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

PEDIATRICIANS—SOUTHERN CALIFORNIA. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

IMMEDIATE OPENING. BC, recently eligible, Internal Medicine. Assume substantial practice in three person group adjacent to Tri-City Hospital, Oceanside, California. Call (619) 724-8683.

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and has an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is a Paramedic Base Station and Training Center, and in addition, has an active Helicopter Service and Regional Poison Center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after April 30, 1991. The University of California is an Affirmative Action/Equal Opportunity Employer.

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SAN FRANCISCO BAY AREA BC/BE INTERNISTS

We are currently seeking highly qualified Internists and subspecialists to complement our energetic Internal Medicine team. Department members provide a full range of medical services for a population of over 200,000 pre-paid health plan members. Recently renovated and expanded medical center facilities are within convenient commuting distance to virtually any bay area city, and the extensive cultural and recreational activities of northern California. As part of our large, multispecialty group practice, you would enjoy an excellent salary, generous fringe benefits, a flexible schedule, and the opportunity for academic affiliation with prestigious local institutions. Send CV to:

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FULL TIME MD POSITION AT THE LEVEL OF ASSISTANT/ASSOCIATE PROFESSOR OF CLINICAL FAMILY PRACTICE available in the Department of Family Practice, University of California, Davis. Must be BC by the American Board of Family Practice with interest, training, and/or experience in administration, teaching, research, academic publication, and Obstetric activities. The position will remain open until May 31, 1991. Send CV with list of three to five references to Robert C. Davidson, MD, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd, Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer.

PEDIATRICIAN—Salt Lake City area. Progressive community, excellent cultural and recreational opportunities. Thriving multispecialty practice or solo practice location. Top remuneration. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

OB/GYN—Salt Lake City area. Progressive community, excellent cultural and recreational activities. Thriving independent practice in multispecialty group location with excellent coverage. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

PRACTICE OPPORTUNITIES. Family Practice, Internal Medicine, and Obstetrics and Gynecology positions available in San Diego, California, Phoenix, Arizona, Seattle, Washington, and Salt Lake City, Utah. Contact Eric Bennett, PO Box 5316, Scottsdale, AZ 85261; (602) 998-4540.

FEMALE PHYSICIAN seeks partner in thriving practice of Primary Care Medicine and office Gynecology. Specializing in personalized health care for women. Located in a delightful, growing community 35 miles from San Francisco. Flexible hours. Contact Bonnie Rathjen, MD, 4102 Moller Dr, Pleasanton, CA 94566; (415) 462-6360 evenings.

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COASTAL SOUTHERN CALIFORNIA. Seeking BC/BE Internist with subspecialty in Oncology to join a fast growing multispecialty group practice in north San Diego county. Generous compensation package; competitive salary, malpractice, medical/dental/life/AD&D/disability; wonderful living environment. Please send CV to Physician Recruitment, The Mission Park Medical Clinic, 2201 Mission Ave, Oceanside, CA 92054; or call (619) 967-4892.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

INTERNIST—Salt Lake City area. Progressive community, excellent skiing, hiking, as well as close proximity to major city. Independent or multispecialty group locations. Outstanding remuneration package. Contact Scott Blakley, Tooele Valley Healthcare System, 211 South 100 East, Tooele, UT 84074; (801) 882-1697.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled, Family Practice or Emergency Physician to join highly respected Urgent Care group with two beautiful Santa Cruz clinics. Committed to high quality care. Nice people, flexible scheduling, comprehensive benefits, including paid malpractice, group health insurance, long-term disability insurance, no nights, rapid advancement to full partnership in an outstanding place to live. Please send CV to Stuart Simon, MD, 6800 Soquel Dr, Aptos, CA 95003; or call (408) 662-3611.

MONTEREY BAY. Immediate opportunity for full-time/part-time Internist/Family Practitioner to join busy, well established and respected group practice. Excellent laboratory and x-ray facilities. Send CV to Thorngate Medical Group, attn. Jean Reynolds, 1011 Cass St, Ste 201, Monterey, CA 93940.

HAWAII. Family Practitioner and Pediatrician needed for rural underserved area. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

THE DIVISION OF FAMILY MEDICINE at the UCSD School of Medicine is recruiting physicians to staff clinical practices and to provide clinical supervision to residents and medical students at a variety of locations in San Diego county. Candidates should be BC in Family Medicine and licensed or eligible for licensure in the state of California. Responsibilities will include direct patient care. Salaries are competitive and commensurate with experience and qualifications. Candidates should send a CV and names of three references to David M. Baughan, MD, Director of Clinical Services, Division of Family Medicine (0807) UCSD, 9500 Gilman Dr, La Jolla, CA 92093-0807. The University of California, San Diego is an Equal Opportunity/Affirmative Action Employer.

NEPHROLOGIST WANTS PARTNER/ASSOCIATE BC/BE Gastroenterologist/Cardiologist/Nephrologist/Pulmonologist. Excellent practice, equal partnership opportunity without buy-in or overhead. Send CV to Dr M. Streger, 27800 Medical Center Rd, Ste 122, Mission Viejo, CA 92691.

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NEWPORT BEACH. Start up opportunity to associate with a busy General Internist. Flexible terms. Please send CV to John Homan, MD, 351 Hospital Rd, #411, Newport Beach, CA 92663; (714) 548-1278.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

BC/BE FAMILY PRACTITIONER, OB-competent, for nonprofit community clinic in California redwood country. Rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

REDWOOD COAST. Primary Physician for community health center providing quality care to low income population. Excellent hospitals, support services. Supervise midlevels. Unequaled life-style combines spectacular beaches and redwoods with amenities of university town. Contact M. Sterling, HODC, 770 10th, Arcata, CA 95521; (707) 822-2957.

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PHYSICIANS WANTED

PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialities for hospitals, clinics, multi-specialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **Nugent & Grant, Inc, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

OREGON. General Internal Medicine and Family Practice, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

WARM AND SUNNY ARIZONA. Thomas-Davis Medical Centers, PC, a rapidly expanding multispecialty group practice of 150 plus physicians in 14 clinic locations throughout Arizona has positions available in Family Practice, Internal Medicine, Otolaryngology, OB/GYN, and Orthopedics. Exceptional fringe benefits, profit sharing, and retirement program. Guarantee for first two years, plus incentive. Early shareholder. Fee-for-service, as well as physician owned HMO. Must be BC/BE. Call or write Bill De Long at Thomas-Davis Medical Centers, PC, PO Box 12650, Tucson, AZ 85732; 1 (800) 658-9166.

SAN FRANCISCO EAST BAY. BE/BC Internist needed to join ten physician Primary Care group practice in beautiful San Ramon Valley area. Excellent opportunity and compensation. Reply in confidence to Number 223, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

TWO INTERNISTS seek an associate BE/BC Internist for busy Internal Medicine group practice located in a community of 60,000. Forty miles from San Francisco. Excellent modern hospital. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

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SACRAMENTO, CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS. Opportunities available in Sacramento for BC physicians in Dermatology, Internal Medicine, Orthopedics, Ophthalmology, Otolaryngology, Psychiatry, Toxicology, and Neurology with a multispecialty medical group which provides forensic medical evaluations. This is an excellent opportunity to supplement income as well as associate with a well respected medical group whose practice is limited to evaluations. Send inquiry and CV to Terence Doyle, Disability Reporters, 2805 J St, Ste 305, Sacramento, CA 95816; (916) 444-8600.

CENTRAL CALIFORNIA. Hospital based teaching opportunity for OB/GYN in a new residency program at the KMC. Ideal candidate is a team player with a strong desire to teach residents. This UCLA affiliate has a busy OB department with 5,000 deliveries per year. Please contact Mary Letterii, Vice President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

FAMILY/GENERAL PRACTICE POSITION. We are looking for a Family/General Practitioner to join a progressive small group practice in Berkeley, California, serving a very diverse patient population. We practice a wide range of adult medicine, general hospital medicine, office Pediatrics and Gynecology. There is no Obstetrics. Work hours are flexible and range from half- to full-time. The starting date and salary are negotiable. Minorities and women encouraged. Contact Linda Spangler, MD, Alcatraz Ave Medical Group, 1650 Alcatraz Ave, Berkeley, CA 94703; (415) 652-8680.

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Rockwood Clinic, PS

E. 400 Fifth Ave
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CENTRAL CALIFORNIA. Anesthesiologist Medical Director needed for high volume teaching hospital. Opportunity to develop contract for services with Kern County. Successful candidate has good track record of leadership with solid clinical background. Please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

INTERNIST. Immediate opening. Large, established, rapidly growing Los Angeles medical facility. High salary. Full benefits. Malpractice insurance paid. Contact Mr Miller; (213) 384-2504.

INTERNIST WANTED. Internal Medicine physician wanted to join an Internal Medicine group in San Diego, California. Guarantee plus commission, opportunity to join full partnership in two years. Reply to Number 231, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNAL MEDICINE—OREGON-COLUMBIA GORGE. Outdoor recreation, a progressive well-equipped hospital, and proximity to Portland make this an exceptional opportunity for a solo General Internist. Hospital offering income guarantee, and start up expenses for two years, plus interview and relocation expenses. Critical care experience required. Ski, boat, fish, hike, and hunt out your back door. For info call Alex Johnson, 1 (800) 327-1585.

FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

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Practice and career opportunities with the nation's largest and most respected physician-managed group practice in managed care. Practice and career opportunities available in major metropolitan and suburban areas for staff positions. For more information, send your CV to:

Irwin P. Goldstein, MD, Associate Medical Director, SCPMG, KAISER PERMANENTE, Department 057, Walnut Center, Pasadena, CA 91188-8013; or call 1 (800) 541-7946.

INTERNAL MEDICINE—NORTHERN CALIFORNIA. Four season recreational area in northern California with mild temperature, offers skiing, boating, and hiking. Six person Primary Care group seeks General Internist with Critical Care expertise. Comprehensive benefits, income guarantee. Call Alex Johnson, 1 (800) 327-1585.

PEDIATRICIAN, BC/BE to join group Family Practice/Pediatrics. Growing community with growing pediatric population. Active Nursery Level II hospital and nursery with NNP coverage. Offering competitive salary, equal call schedules, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 13-18, 1992, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 20-22, 1991, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-13, 1991, Westin Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-27, 1991, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-4, 1991, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1991, Quail Lodge, Carmel, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-10, 1991, The Marshall Building, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): April 26-28, 1991, Salisham.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 11-13, 1991, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, 1991, Red Lion, Bellevue.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 13-15, 1991, Jackson Lake Lodge, Moran.

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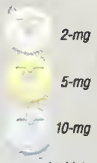

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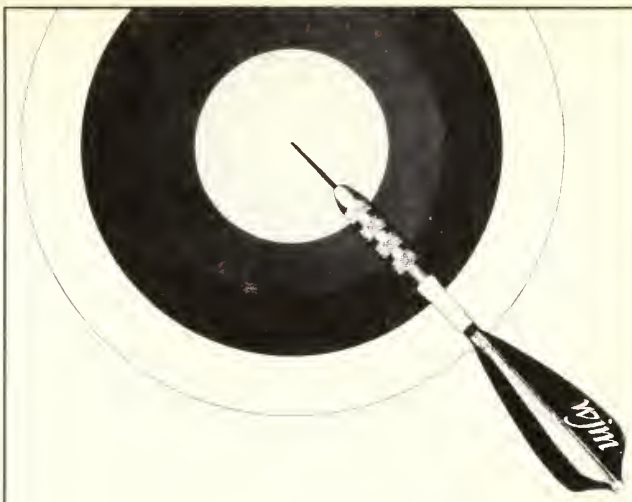

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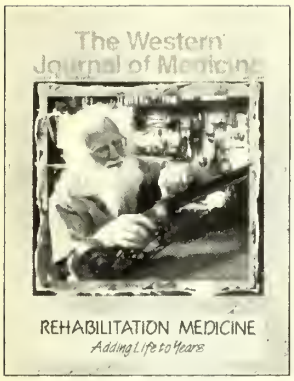

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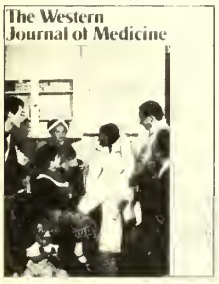

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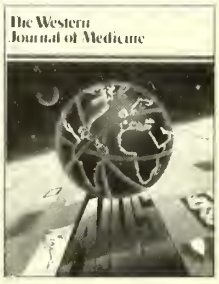

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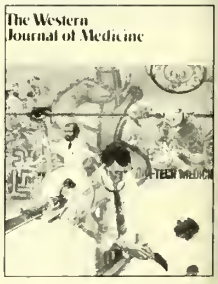

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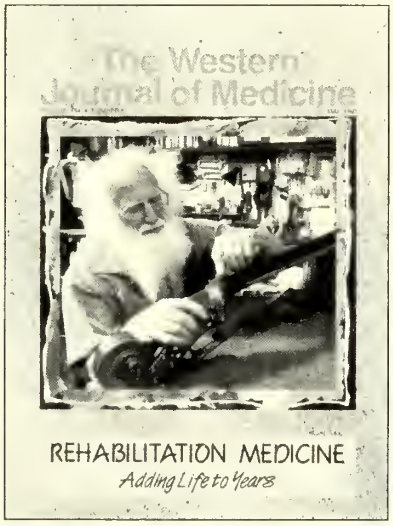

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From the Comprehensive Rehabilitation Center, Edward Hines Jr Veterans Affairs Hospital, Hines, and the Departments of Orthopedics and Rehabilitation, Loyola University Medical Center, Maywood, Illinois.

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NANCY BECKER KENNEDY

Ms Kennedy is an award-winning free-lance writer and producer for public television in Los Angeles, California.

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ANNOUNCING A GREAT YEAR AHEAD FOR HERPES PATIENTS

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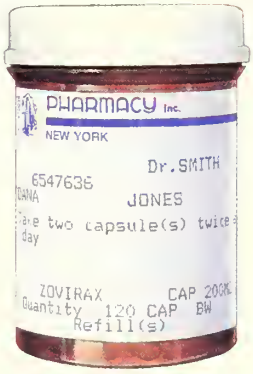

* Alternate maintenance regimens range from 200 mg t.i.d. to 200 mg five times daily.

†In a controlled study of 3 years' duration, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively.[3]

Please see brief summary of prescribing information on adjacent page.

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KEEPS HERPES PATIENTS LESION-FREE LONGER†

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BRIEF SUMMARY

INDICATIONS AND USAGE: Zovirax Capsules and Suspension are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients

Zovirax Capsules and Suspension are also indicated for the acute treatment of herpes zoster (shingles)

Genital Herpes Infections: The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs Thus orally administered Zovirax is not appropriate in treating all genital herpes infections The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes)

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing The duration of pain and new lesion formation was decreased in some patient groups The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy Patients with mild disease may derive less benefit than those with more severe episodes In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax

Recurrent Episodes:

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered Zovirax given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively Serial analyses of the 3 month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time

The frequency and severity of episodes of untreated genital herpes may change over time After 1 year of therapy the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects In general, orally administered Zovirax should not be used for the suppression of recurrent disease in mildly affected patients Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease Thus, this regimen should be considered only for appropriate patients with annual re-evaluation

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions

Herpes Zoster Infections: In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to Zovirax and 94 to placebo), Zovirax (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to Zovirax and 43 to placebo), Zovirax (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia)

CONTRAINDICATIONS: Zovirax Capsules and Suspension are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations

WARNINGS: Zovirax Capsules and Suspension are intended for oral ingestion only

PRECAUTIONS General: Zovirax has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility) The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION)

Exposure of Herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients The relationship between the *in vitro* sensitivity of Herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY-Microbiology)

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve Urinary excretion and renal clearance were correspondingly reduced The clinical effects of this combination have not been studied

Carcinogenesis, Mutagenesis, Impairment of Fertility The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes) Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics)

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay

Acyclovir was tested in two *in vitro* cell transformation assays Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters, higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels) In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels) In all 4 microbial assays, no evidence of mutagenicity was observed Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in man At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels Results in the other five mammalian cell loci follow at 3 loci in a Chinese hamster ovary cell line the results were inconclusive at concentrations at least 1850 times human levels, at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p o) or in rats (25 mg/kg/day, s c) In the mouse study plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels At a higher dose in the rat (50 mg/kg/day s c), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels) No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels) In a rat peri- and postnatal study at 50 mg/kg/day s c (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12 5 mg/kg/day and 25 mg/kg/day, s c The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured) However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively caused testicular atrophy Plasma levels were not measured in the one month study and were 24 to 48 times human levels in the six month study Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day, some evidence of recovery of sperm production was evident 30 days postdose Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels No testicular abnormalities were seen in dogs given 50 mg/kg/day i v for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels)

Pregnancy: ***Teratogenic Effects***: Pregnancy Category C Acyclovir was not teratogenic in the mouse (450 mg/kg/day p o), rabbit (50 mg/kg/day, s c and i v) or in standard tests in the rat (50 mg/kg/day, s c) These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity In this test, rats were given 3 s c doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels There are no adequate and well-controlled studies in pregnant women Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of Zovirax and ranged from 0 6 to 4 1 times corresponding plasma levels These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0 3 mg/kg/day Caution should be exercised when Zovirax is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Herpes Simplex, ***Short-Term Administration***: The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with orally administered Zovirax were nausea and/or vomiting in 8 of 298 patient treatments (2 7%) and headache in 2 of 298 (0 6%) Nausea and/or vomiting occurred in 2 of 287 (0 7%) patients who received placebo

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with orally administered Zovirax (0 3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash leg pain, inguinal adenopathy, medication taste and sore throat

Long-Term Administration: The most frequent adverse reactions reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 Zovirax - treated patients were nausea (4 8%), diarrhea (2 4%), headache (1 9%) and rash (1 7%) The 589 control patients receiving intermittent treatment of recurrences with Zovirax for 1 year reported diarrhea (2 7%), nausea (2 4%), headache (2 2%) and rash (1 5%)

The most frequent adverse reactions reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1 5%), rash (1 3%) and paresthesia (0 8%) Reactions reported by 329 patients during the third year include asthenia (1 2%), paresthesia (1 2%) and headache (0 9%)

Herpes Zoster The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral Zovirax 5 times daily for 7 to 10 days in 323 patients were malaise (11 5%), nausea (8 0%), headache (5 9%), vomiting (2 5%), diarrhea (1 5%) and constipation (0 9%) The 323 placebo recipients reported malaise (11 1%), nausea (11 5%), headache (11 1%) vomiting (2 5%), diarrhea (0 3%) and constipation (2 4%)

OVERDOSAGE: Precipitation of acyclovir in renal tubules may occur when the solubility (2 5 mg/mL) in the intratubular fluid is exceeded Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species rats treated with i v and i p doses of 20 mg/kg/day for 21 and 31 days respectively, and at s c doses of 100 mg/kg/day for 10 days, rabbits at s c and i v doses of 50 mg/kg/day for 13 days, and dogs at i v doses of 100 mg/kg/day for 31 days A 6 hr hemodialysis results in a 60% decrease in plasma acyclovir concentration Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION)

DOSAGE AND ADMINISTRATION Treatment of initial genital herpes: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 10 days

Chronic suppressive therapy for recurrent disease: 400 mg (two 200 mg capsules or two teaspoonfuls [10 mL] suspension) 2 times daily for up to 12 months, followed by re-evaluation See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily

Intermittent Therapy: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 5 days Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules or four teaspoonfuls [20 mL] suspension) every 4 hours orally 5 times daily for 7 to 10 days

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications

Normal Dosage Regimen (5x daily)	Creatinine Clearance (mL/min/1 73m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval (hrs)
200 mg every 4 hours	> 10	200	every 4 hours 5x daily
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

For patients who require hemodialysis, the dosing schedule should be adjusted so that a dose is administered after each dialysis

References: 1. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection: a multicenter double-blind trial. *JAMA*. 1988;260:201-206. **2.** Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med*. 1988;85(suppl 2A):14-19. **3.** Data on file, Burroughs Wellcome Co., 1990.

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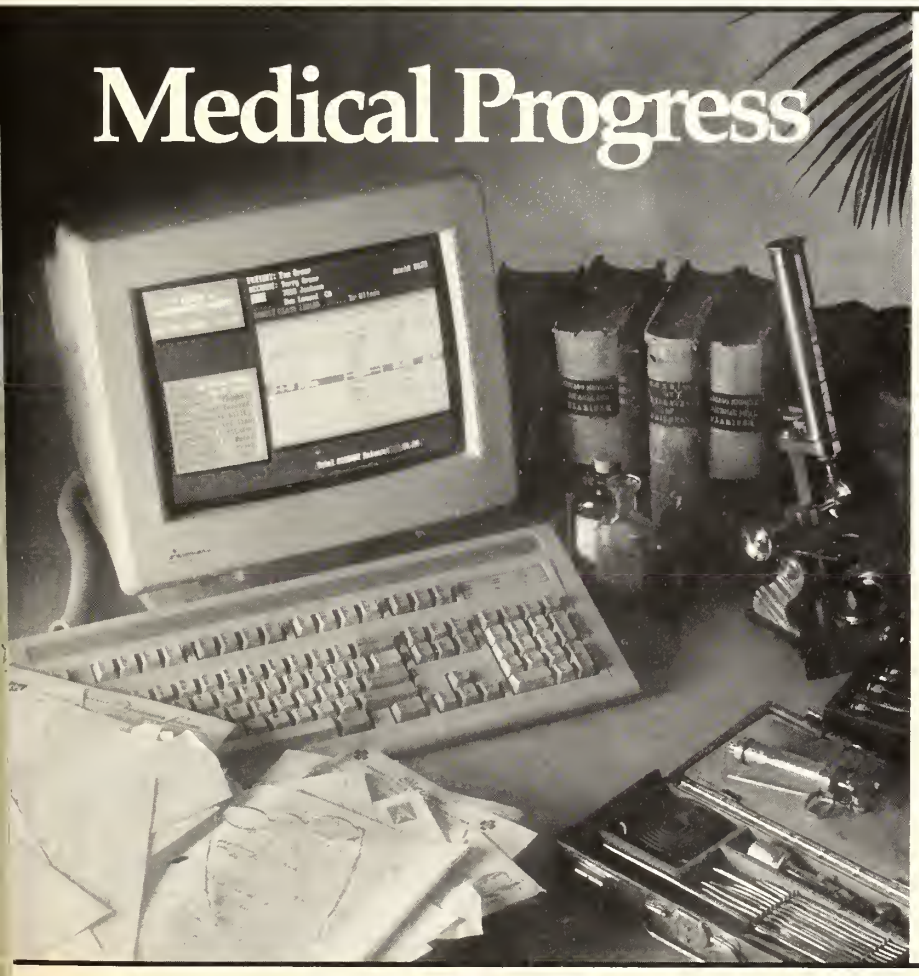

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BARBARA FAYE WAXMAN
Ms Waxman is a student in the graduate school of Architecture and Urban Planning at the University of California, Los Angeles.

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Ms Rousso is Director of Disabilities Unlimited Psychotherapy and Consultative Services, New York, and a member of the New York City Human Rights Commission.

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MARSHA SAXTON, MS
Ms Saxton is Executive Director of the Project on Women and Disability in Boston, Massachusetts.

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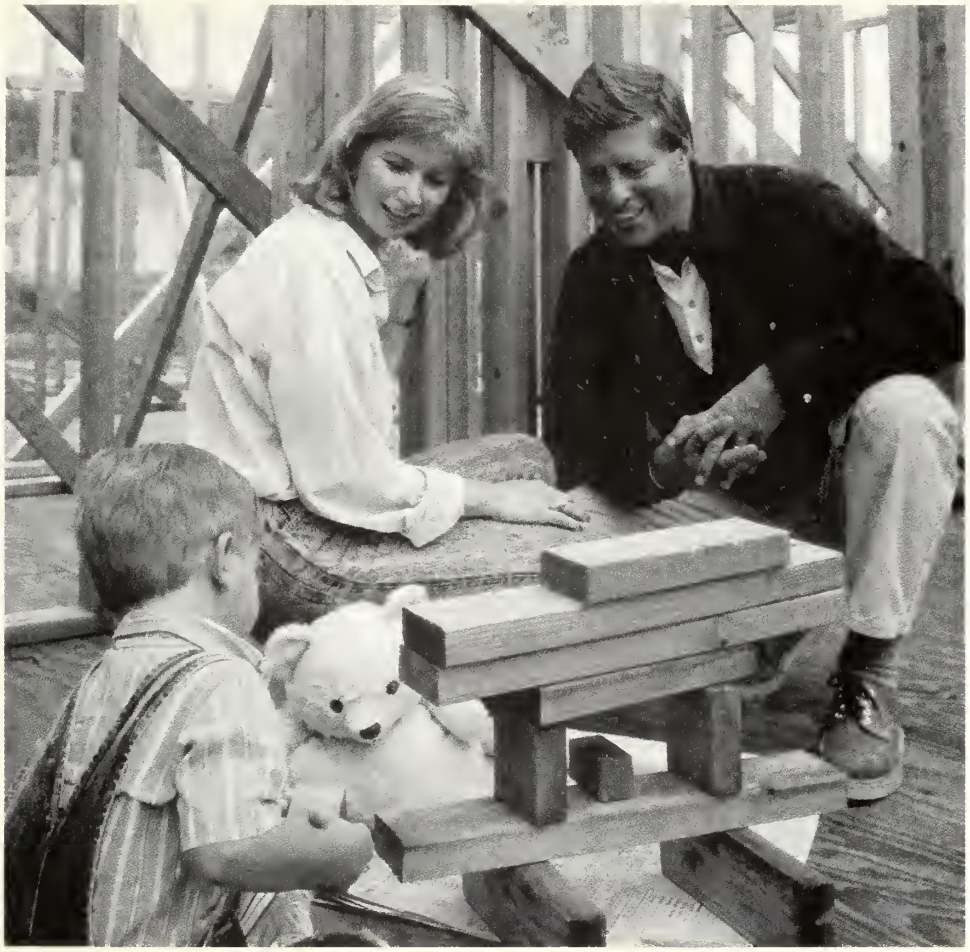

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

May 11—**HIV/AIDS: An Update for Physicians, Dentists and Pharmacists.** ADHS, MAHEC, ArMA, and the University of Arizona College of Medicine at the Pointe at Squaw Peak, Phoenix. Sat. Contact: Mary Anne Barnes, (602) 246-8901.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724 (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 16-19—**California Society of Anesthesiologists Annual Meeting.** CSA at Marriott Hotel, Anaheim. Thurs-Sun. 20 hrs. $175. Contact: CSA, 1065, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

September 7-8—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Horizon Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, Ste 410, Foster City. (800) 345-3691.

CARDIOLOGY

June 21-22—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 1-3—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

August 2-4—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Hotel, Monterey. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 16-18—**Cardiac Diagnostic Methods and Risk Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

October 10-12—**Cardiology Update: 1991.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. 12.5 hrs. $440. Contact: ACC, Extramural Programs, Dept 5080, Washington, DC 20061-5080. (800) 253-4636.

October 17-19—**Tenth Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $395. Contact: UCSF.

October 18-19—**Coronary Heart Disease Update.** Medical Education Resources at Parc Fifty Hotel, San Francisco. Fri-Sat. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

DERMATOLOGY

May 18-19—**Advanced Dermatologic Surgery Workshop.** UCLA at the Dermatologic Surgery Center, Los Angeles. Sat-Sun. 15 hrs. $800. Contact: UCLA.

July 11-14—**Advanced Seminars in Dermatology.** UCSF at Quail Valley Lodge, Carmel. Thurs-Sun. Contact: UCSF.

July 16-20—**Dr. Hugh Greenway's Seventh Annual Conference: Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation/UCSD at Scripps Clinic, La Jolla. Tues-Sat. 36 hrs. $1100. Contact: Susan J. Buntjer, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

July 19-21—**Contact Dermatitis: The Basics.** Stanford at Hotel Meridien, San Francisco. Fri-Sun. Contact: Pamela Bain, Dept of Dermatology, Room R-122, Stanford 94305. (415) 723-7854.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

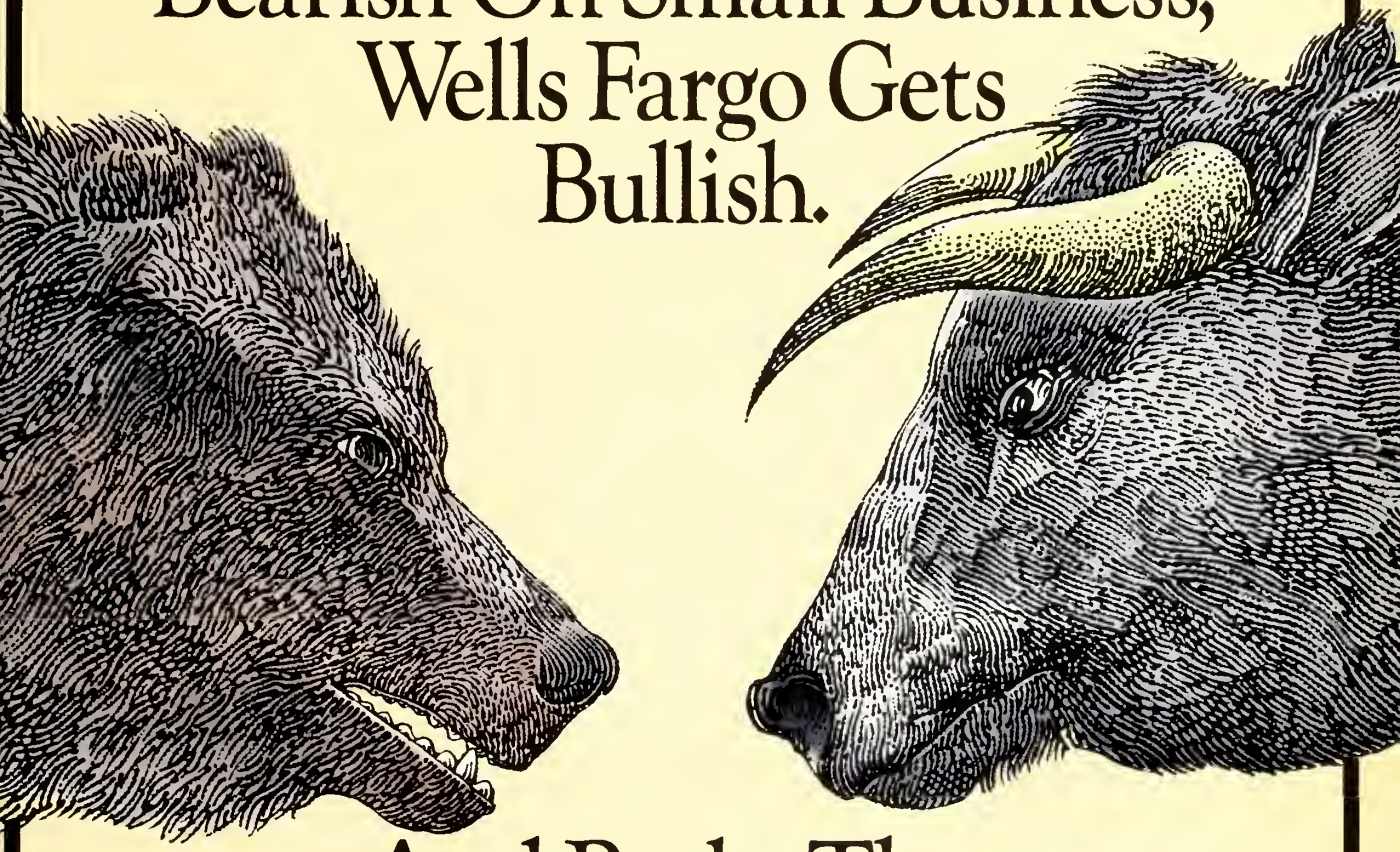
UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 506)

While Other Banks Get Bearish On Small Business, Wells Fargo Gets Bullish.



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(Continued from Page 504)

August 16-20—**Fifth Annual Hot Spots in Dermatology: Masters Under the Mango Trees.** The Hawaii Dermatology Society and the Kauai Foundation at the Kaluakoi Hotel, Kepuhi Beach, Molokai, Hawaii. Fri-Tues. Contact: David Elpern, MD, Box 457, Kalaheo, HI 96741. (808) 245-1505.

EMERGENCY MEDICINE

June 8-9—**Clinical Toxicology and Emergency Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Sat-Sun. 16 hrs. $310. Contact. UCSF.

June 24-28—**Postgraduate Institute for Primary Care & Emergency Physicians Emergency Medicine Symposium III: Pediatrics, OB/GYN, Dermatology, Legal Aspects, Etc.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $260-$485. Contact: UCSD.

August 1-3—**Debates and Updates in Pediatric Emergency Medicine.** UCSF at San Francisco Hilton Hotel, San Francisco. Thurs-Sat. 16 hrs. Contact: UCSF.

August 7-11—**Wilderness Medicine: '91.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Program Director, Box 321, Yreka 96097. (800) 888-5632.

August 19-23—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott, La Jolla. Mon-Fri. 32 hrs. $485. Contact: UCSD.

August 23-26—**Advances in Emergency Medicine.** Kaiser Permanente at Grand Hyatt Wailea Resort and Spa, Maui, Hawaii. Fri-Mon. Contact: Pat Salber, MD, Kaiser Permanente Hospital, 2200 O'Farrell, San Francisco 94115-3395.

October 28-November 1—**Twentieth Annual Topics in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $510. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

May 28-June 1—**Eighteenth Annual Joint UCLA-Santa Monica Hospital Medical Center Family Practice Refresher Course.** UCLA Extension at Miramar Sheraton Hotel, Santa Monica. Tues-Sat. 32 hrs. $445. Contact: UCLA.

June 9-14—**Fingers to the Toes: Orthopaedics for the Primary Care Physician.** UCD at Stanford Sierra Camp, Fallen Leaf Lake, South Lake Tahoe. Sun-Fri. 29 hrs. Contact: UCD.

June 10-14—**UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Costa Mesa. Mon-Fri. Contact: UCI.

July 8-11—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

August 23-25—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

October 2-4—**Sixth Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 19 hrs. $465. Contact: UCSF.

October 18-20—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

May 13-17—**Advances in Internal Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $585. Contact: UCSF.

May 25-27—**1991 CSIM Annual Meeting: Controversies, Challenges, Changes, and Calamari.** CSIM at Monterey Plaza Hotel. Sat-Mon. Contact: Cynthia Eaton, CSIM, Box 880606, San Francisco 94188-0606. (415) 882-5198.

June 15—**Lyme Disease Symposium.** Kaiser Permanente Northern California at El Rancho Tropicana Convention Center, Santa Rosa. Sat. 5 hrs. Contact: Joyce Appelbaum, 1950 Franklin, Oakland 94612. (415) 987-4726.

August 26-28—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

August 26-30—**Internal Medicine Board Review.** Stanford University Medical Center. Mon-Fri. Contact: STAN.

September 20-22—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sun. 18 hrs. $420. Contact: UCSF.

September 28—**Pain: Diagnosis, Treatment and Management.** Scripps Clinic and Research Foundation, La Jolla. Sat. 19 hrs. $75. Contact: Laurel Steigerwald, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

October 14-20—**Seventeenth Annual Lymphoma Course.** Scripps Clinic and Research Foundation, La Jolla. Mon-Fri. 25 hrs. $550. Contact: Laurel Steigerwald, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

OB/GYN

May 17-18—**Fundamentals of Obstetrical Ultrasound.** Memorial/UCI Center for Health Education. Fri-Sat. Contact: UCI.

August 9-11—**4th Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: Memorial/UCI Center for Health Education, Box 1428, Long Beach 90801. (213) 595-3811.

August 16-18—**Office Gynecology for the Primary Care Physician.** San Diego State University at the Hyatt Islandia, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

OCCUPATIONAL/ENVIRONMENTAL

May 30-31—**Tenth Annual Occupational and Environmental Medicine Symposium.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thurs-Fri. 18 hrs. $155. Contact: UCD.

October 21-November 1—**Occupational and Environmental Medicine: Session II.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

October 28-November 1—**Advances in Occupational and Environmental Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600 Contact: UCSF.

OPHTHALMOLOGY

May 17-19—**California Association of Ophthalmology Annual Meeting.** CAO at Sheraton Grande Torrey Pines, La Jolla. Fri-Sun. Contact: Linda Xyz. (415) 777-3937.

October 13-17—**Joint Meeting of the American Academy of Ophthalmology and Pan-American Association of Ophthalmology** at Anaheim Convention Center. Sun-Thurs. Contact: AAO, PO Box 7424, San Francisco 94120. (415) 561-8500.

PATHOLOGY

May 23-24—**Current Issues in Anatomic Pathology.** UCSF at Union Square Holiday Inn, San Francisco. Thurs-Fri. 12 hrs. $325. Contact: UCSF.

July 15-19—**Advances in Gastroenterology.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 19-22 hrs. $425. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 9-10—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684

October 12—**Thirty-first Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott, La Jolla. Sat. Contact: Sylvie Tarro, (213) 641-8152.

PEDIATRICS

May 16-18—**24th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 1—**Special Children: Pediatric Perspectives in the '90s.** Children's Hospital at Merritt Peralta Health Education Center, Oakland. Sat. 7 hrs. $150. Contact: Kim Leadon, Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

June 21-23—**Current Concepts in Child Neurology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 15 hrs. Contact: Children's Hospital, (619) 576-4072.

August 19-21—**Pediatrics Update: 1991.** San Diego State University at the Hyatt Islandia, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 638)

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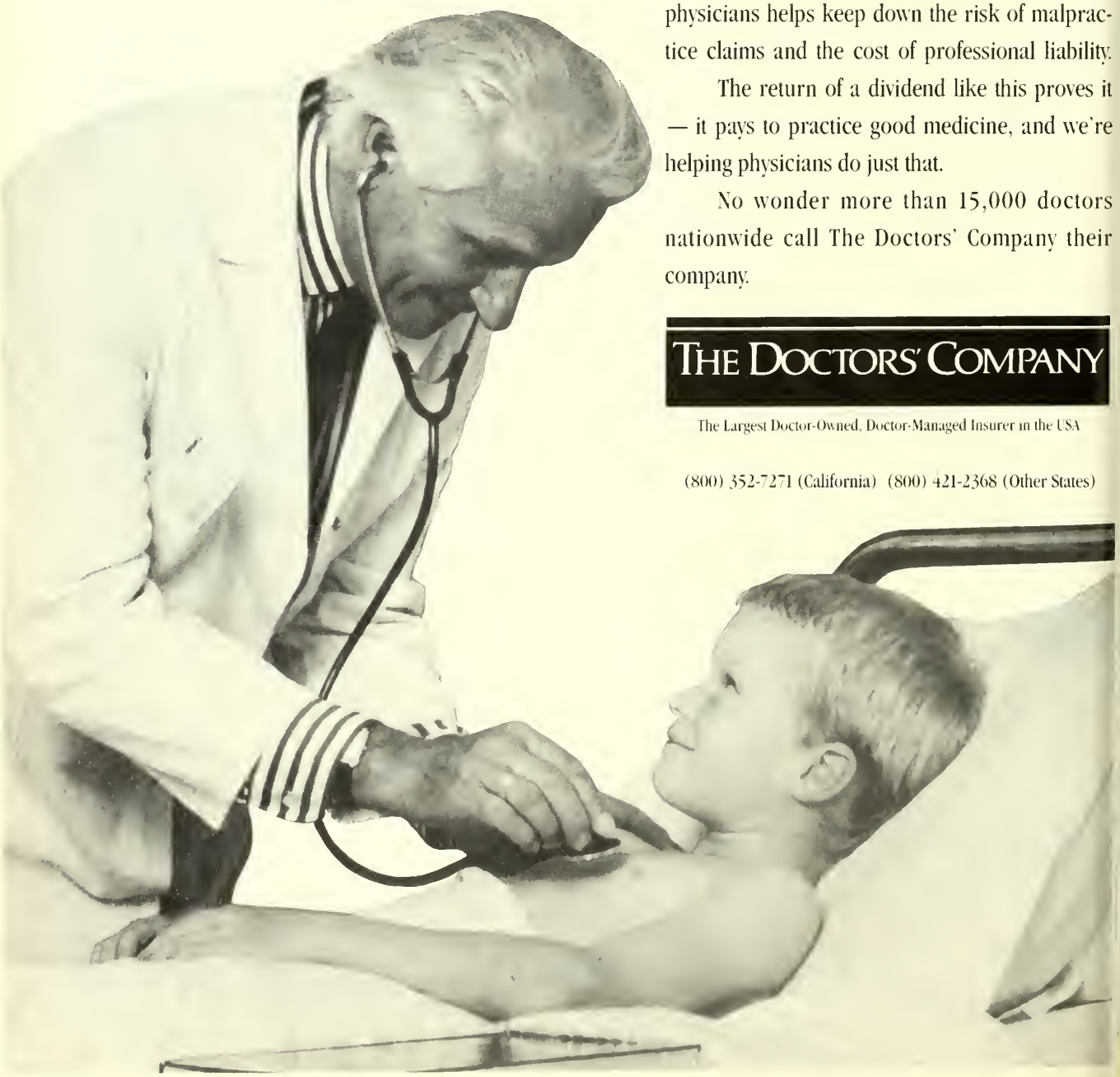
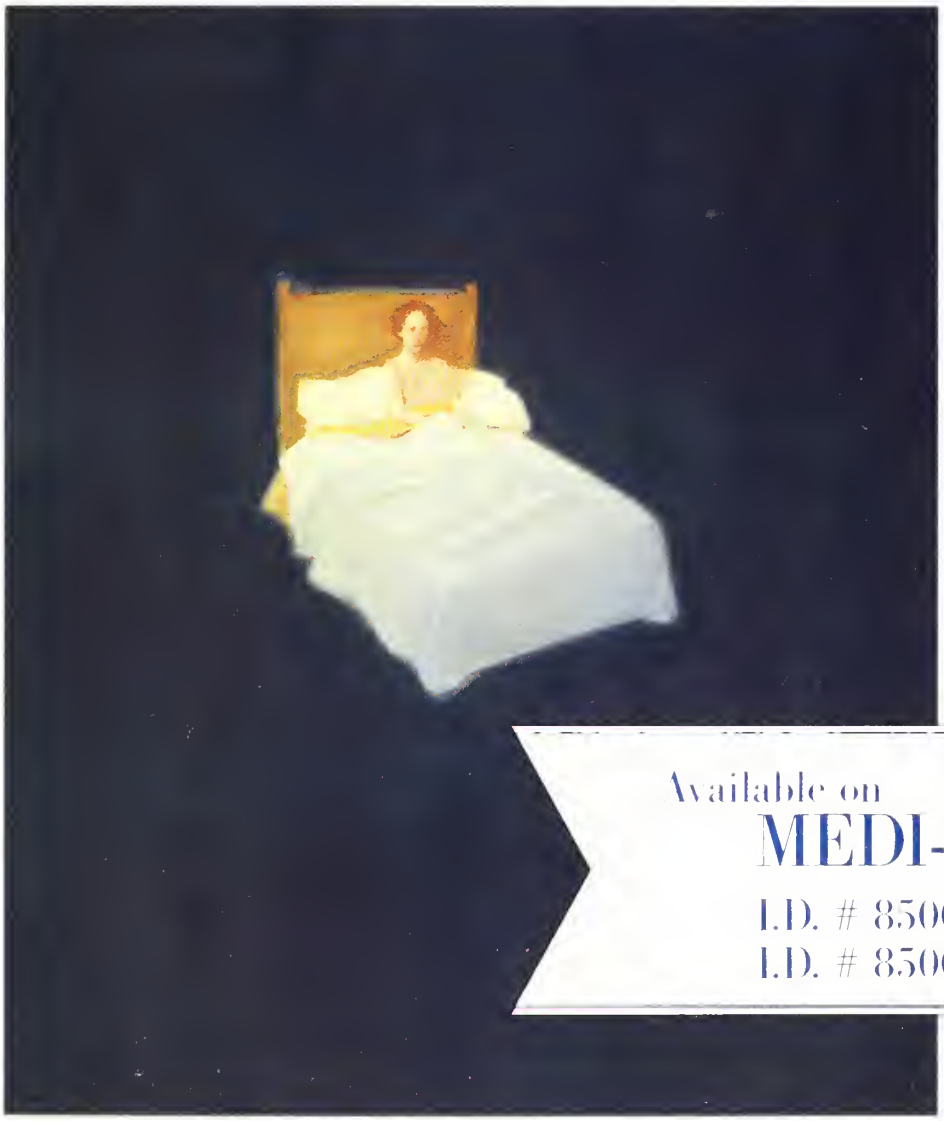


Finally, for patients who dream of sleep...



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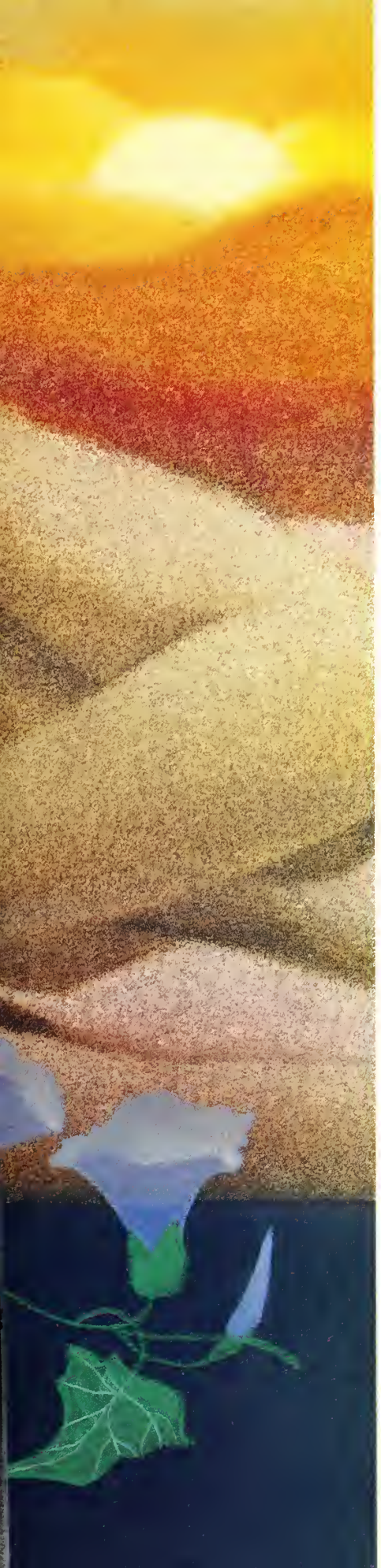

The sleep of their dreams

A rapid, yet gentle onset

Clinical studies have demonstrated that ProSom initiates sleep within 15 to 30 minutes after bedtime.[1,2] Patients' responses in both short- and long-term sleep laboratory and outpatient efficacy studies indicated significant improvements in their ability to fall asleep.[1-3]

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ProSom provides an average of 6 to 8 hours of improved sleep, with a significant reduction in nocturnal awakenings and wake time during sleep.[1-5] In fact, throughout multiple, independent efficacy studies, ProSom was shown to significantly improve *every* measure of sleep.[1-5]

A clear return to morning

Daytime performance with ProSom was shown to be comparable to placebo-treated patients, with performance deficits, if any, shown to be short and transient.[6] And clinical studies, including a 10-week efficacy trial, demonstrated no anterograde amnesia or short-term memory impairment.[6,7]

NEW

ProSom™
estazolam CIV

When sleep doesn't come naturally

Please see brief summary of prescribing information on following page.

NEW

ProSom™ estazolam Ⓘv

The sleep of their dreams

- A rapid, yet gentle onset
- A full night's duration
- A clear return to morning

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ProSom
2mg
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References:

1. Lamphere J, Roehrs T, Zorick F, Koshorek G, Roth T. Chronic hypnotic efficacy of estazolam. *Drugs Exp Clin Res* 1986;12(8):687-691.
2. Pierce MW, Shu VS. Efficacy of estazolam: The United States clinical experience. *Am J Med* 1990;88(3A):6S-1
3. Walsh JK, Targum SD, Pegram V, et al. A multi-center clinical investigation of estazolam: short-term efficacy. *Curr Ther Res* 1984;36(5):866-874.
4. Dominguez RA, Goldstein BJ, Jacobson AF, Steinbook RM. Comparative efficacy of estazolam, flurazepam, and placebo in outpatients with insomnia. *J Clin Psychiatry* 1986;47(7):362-365.
5. Roehrs T, Zorick F, Lord N, Koshorek GL, Roth T. Dose-related effects of estazolam on sleep of patients with insomnia. *J Clin Psychopharmacol* 1983;3(3):152-156.
6. Pierce MW, Shu VS, Groves LJ. Safety of estazolam: The United States clinical experience. *Am J Med* 1990;88(3A):12S-17S.
7. Schart MB, Mayleben DW, Fletcher KA, Shu VS, Pierce MW. Effect of single doses of estazolam and triazolam memory function in adult insomniacs. Submitted for publication.

Brief Summary

CLINICAL PHARMACOLOGY:

The range of estimates for the elimination half-life varied from 10 to 24 hours. Benzodiazepine clearance is accelerated in smokers compared to nonsmokers, and there is evidence that this occurs with estazolam. This decrease in half-life, presumably due to enzyme induction by smoking, is consistent with other drugs with similar hepatic clearance characteristics. In all subjects the mean elimination half-life appears to be independent of the dose.

CONTRAINDICATIONS:

Contraindicated in pregnant women due to potential fetal damage. Women of childbearing age should be warned the potential risk to the fetus.

WARNINGS:

Due to CNS-depressant effects patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and about possible combined effects with alcohol and other CNS-depressant drugs.

As with all benzodiazepines, amnesia, paradoxical reactions, and other adverse behavioral effects may occur.

There have been reports of withdrawal symptoms of the type associated with CNS depressants following rapid decrease or abrupt discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

PRECAUTIONS:

General. Impaired motor and/or cognitive performance attributable to accumulation of benzodiazepines and active metabolites is a concern in certain patients (eg, those sensitive to benzodiazepines or those with a reduced capacity to metabolize and eliminate them) (see DOSAGE AND ADMINISTRATION). Elderly or debilitated patients and those with impaired renal or hepatic function should be advised to monitor themselves for signs of excessive sedation or impaired conditions.

May cause dose-related respiratory depression that is ordinarily not clinically relevant at recommended doses in patients with normal respiratory function. Monitor patients with compromised respiratory function appropriately.

Administered with caution to patients exhibiting symptoms of depression. Suicidal tendencies and intentional overdosage is more common in such patients.

Information for Patients. Inform patients about consumption of alcohol and other drugs, possible fetal damage and excretion in breast milk, hazards of operating machinery or driving, not increasing dose, and worsening of sleep after abrupt discontinuation.

Laboratory Tests. Not ordinarily required in healthy patients. When treatment is protracted, periodic blood count, urinalysis, and blood chemistry analyses are advisable.

Drug Interactions. Benzodiazepines may be potentiated by anticonvulsants, antihistamines, alcohol, barbiturates, monoamine oxidase inhibitors, narcotics, phenothiazines, psychotropic medications, or other drugs that produce CNS depression. Smokers have increased clearance of benzodiazepines (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis, Impairment of Fertility. Two-year carcinogenicity studies were conducted in mice and rats at doses of 0.8, 3, and 10 mg/kg/day and 0.5, 2, and 10 mg/kg/day, respectively. Evidence of tumorigenicity was not observed. Hyperplastic liver nodules were increased in female mice given mid- and high doses. The significance of such nodules in mice is not known. *In vitro* and *in vivo* mutagenicity tests did not show a mutagenic potential. Fertility in male and female rats was not affected by doses up to 30 times the usual recommended human dose.

Pregnancy. May cause fetal damage if administered during pregnancy. The child born of a mother taking benzodiazepines may be at risk for withdrawal symptoms and neonatal flaccidity during the postnatal period.

Labor and Delivery. No established use.

Nursing Mothers. Use in nursing mothers is not recommended.

Pediatric Use. Safety and effectiveness below the age of 18 not established.

Geriatric Use. Approximately 18% of patients studied were 60 years or older. The adverse event profile did not differ from that observed in younger individuals. Exercise care when prescribing to small or debilitated elderly patients (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS:

During clinical trials in which ProSom was administered to 1277 patients, the most commonly observed adverse events were somnolence, hypokinesia, dizziness, and abnormal coordination. The events listed below were also observed. Although these events occurred during treatment with ProSom, they were not necessarily caused by it.

Body as a Whole: abdominal pain, allergic reaction, asthenia, back pain, body pain, chest pain, chills, edema, fever, headache, jaw pain, lower extremity pain, malaise, neck pain, swollen breast, upper extremity pain. *Cardiovascular System:* arrhythmia, flushing, palpitation, syncope. *Digestive System:* constipation, decreased appetite, dry mouth, dyspepsia, enterocolitis, flatulence, gastritis, increased appetite, melena, mouth ulceration, nausea, vomiting. *Endocrine System:* thyroid nodule. *Hematologic and Lymphatic System:* leukopenia, purpura, swollen lymph nodes. *Metabolic/Nutritional Disorders:* increased SGOT, thirst, weight gain, weight loss. *Musculoskeletal System:* arthralgia, arthritis, muscle spasm, myalgia, stiffness. *Nervous System:* agitation, amnesia, anxiety, apathy, ataxia, circumoral paresthesia, confusion, coordination abnormal, decreased libido, decreased reflexes, depression, dizziness, dream abnormal, emotional lability, euphoria, hallucinations, hangover, hostility, hypokinesia, nervousness, neuritis, nystagmus, paresthesia, seizure, sleep disorder, somnolence, stupor, thinking abnormal, tremor, twitch. Minor changes in EEG patterns, usually low-voltage fast activity, were observed during therapy or withdrawal and are of no known clinical significance. *Respiratory System:* asthma, cold symptoms, cough, dyspnea, epistaxis, hyperventilation, laryngitis, pharyngitis, rhinitis, sinusitis. *Skin and Appendages:* acne, dry skin, pruritis, rash, sweating, urticaria. *Special Senses:* abnormal vision, decreased hearing, diplopia, ear pain, eye irritation, eye pain, eye swelling, perverse taste, photophobia, scotomata, tinnitus. *Urogenital System:* frequent urination, hematuria, menstrual cramps, nocturia, oliguria, penile discharge, urinary hesitancy, urinary incontinence, urinary urgency, vaginal discharge/itching. *Postintroduction Reports:* Voluntary reports from non-US postmarketing experience have included rare occurrences of photosensitivity and agranulocytosis. Due to the uncontrolled nature of these reports, a casual relationship has not been determined.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance: Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuation of benzodiazepines. Symptoms range from mild dysphoria and insomnia to abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. Patients with a history of seizures are at increased risk. Withdraw gradually in patients taking benzodiazepines for a prolonged period. Monitor addiction-prone patients closely.

DOSAGE AND ADMINISTRATION:

Initial dose for adult and healthy elderly patients is 1-2 mg at bedtime. Increase dose carefully in the elderly. Consider an initial dose of 0.5 mg in small or debilitated older patients.

HOW SUPPLIED:

Available in 1 mg and 2 mg scored tablets.

Store below 86°F (30°C).

Revised January, 1991

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10239

REHABILITATION MEDICINE *Adding Life to Years*

Out of Sight But Not Out of Hope

WE DECIDED TO BRING a neglected subject into sight and into mind with this, the 12th annual special issue of THE WESTERN JOURNAL OF MEDICINE. "Rehabilitation Medicine—Adding Life to Years," presents a rich array of subjects. Some are serious, others less so; all are written with an intensity that only experience can bring. The authors, who know rehabilitation by accident or by intention, were masterfully chosen by the special editor, Julie G. Madorsky, MD.* They have been willing to write and rewrite in response to peer reviewers' and editors' blandishments. They have poured data, ideas, convictions, and feelings into their papers. We are grateful for their hard work.

Readers will find anger and anguish in this issue; they will understand more about control and loss of control. They will have moments of dread and moments of relief, moments of "There but for the grace of God. . . ." They will feel the chill of despair that leads to tragic decisions. Readers will note fiscal poverty in the field—lack of funds for research and lack of funds for aids that allow function and independence—but no poverty of spirit or determination. Readers will warm to bountiful expressions of love and care and caring. They will learn about effective teamwork. They will be struck by the resourcefulness and courage of investigators and patients. They will smile and share triumphs. Above all, readers will be refreshed by hope.

Aristotle asserted that hope is a waking dream. Samuel Johnson referred to the phantoms of hope. Shakespeare described it more tangibly: "True hope is swift, and flies with swallow's wings."[1] Nathaniel Hawthorne retold the tale of Pandora who, unquenchably curious, opened a forbidden box, unloosing the whole family of troubles upon the world. Cares, sorrows, diseases, pain flew out and settled forever among humankind. Yet there was one last thing left in the box, something sweet, something that shimmered because it was made partly of tears and smiles. Pandora finally unleashed Hope, who said, "As long as you need me . . . I promise never to desert you. There may come times and seasons, now and then, when you think that I have utterly vanished. But again and again, when perhaps you least dream of it, you shall [find me]."[2] To its core, this special issue of the journal is about hope: fuel for discovery, for progress, for healing.

LINDA HAWES CLEVER, MD

REFERENCES

1. Shakespeare W: *The Tragedy of King Richard the Third*. Act 5, scene 2, line 23

2. Hawthorne N: *The Paradise of Children*. Junior Classics Vol 2. Collier & Son, 1912

*Dr Madorsky is Program Medical Director at Casa Colina Hospital for Rehabilitative Medicine, Pomona, California, and Clinical Associate Professor, Department of Physical Medicine and Rehabilitation, University of California, Irvine, College of Medicine. She was named 1988 Physician of the Year by the President's Committee for Employment of Persons With Disabilities. She is a fellow of the American Academy of Physical Medicine and Rehabilitation and a member of the American Congress of Rehabilitation Medicine. Dr Madorsky had polio at age 2; her own life has led to her interest in rehabilitation care. She uses a three-wheeled electric cart around the hospital for long-distance mobility, speed, and endurance.

Rehabilitation Medicine—A Blossom Among Ashes

ONE RESULT of caring for the wounded and disabled soldiers of World War I was the recognition that certain physical measures rarely used in civilian medicine were beneficial in diagnosing and treating a variety of disabling conditions. In 1921 this observation stimulated the American Medical Association to establish the first organization of physicians interested in the use of physical modalities for diagnosis and treatment.[1] And so, the specialty of Physical Medicine arose from the ashes of World War I, with a dedication to enhance the physical capabilities of those who otherwise would be doomed to join the ranks of the invalids, cripples, shut-ins, and shut-outs of society. By 1938 the term physiatrist was coined to identify physicians specializing in Physical Medicine.

During World War II, a call went out to physicians "to rescue profoundly disabled men and women from the human scrap heap and to return them to the community as useful and respected citizens."[2] Thus, the mission of the specialty broadened from the restoration of mobility and physical capabilities to the accomplishment of the highest possible levels of health, emotional well being, independence, and productivity to meet the needs of patients with physical impairments. This expansion in the scope of responsibility was accompanied in 1945 by the transformation of the name of the specialty to Physical Medicine and Rehabilitation. And in 1967, to emphasize physiatrists' partnership with other physicians as well as with allied health professionals, the multidisciplinary American Congress of Rehabilitation Medicine was founded.

Our goal in compiling this special issue of THE WESTERN JOURNAL OF MEDICINE is to present the insights and the evolving processes of Rehabilitation Medicine in a way that will make them relevant to the concerns, dilemmas, and the lives of most physicians and their patients. We are indebted to all who have contributed to this issue—physicians, therapists, nurses, sociologists, psychologists, researchers, attorneys, historians, writers, poets, civil rights activists, and students. Many of them have reached high levels of achievement not in the absence of, but in the face of catastrophic physical disabilities of their own. They exemplify the realization of the enormous possibilities inherent in each individual.

In Israel there is a rare cactus plant that has an exquisitely beautiful flower. The flower is called Queen of the Night because it blooms in the darkest part of the night. When the blackness is deepest, the Queen of the Night comes bursting out.[3] Rehabilitation Medicine is like that flower, blossoming in the dark night of despair. Rehabilitation enables and ennobles persons to transcend disasters of war, deformity, and disability to shine forth in resiliency, mastery, and achievement.

We all know people whom sorrow made bitter. We dedicate this issue to those people whom sorrow made better.

JULIE GEIGER MADORSKY, MD
Special Editor

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Physicians With Disabilities

BARRY CORBET, *Golden, Colorado, and* JULIE G. MADORSKY, MD, *Pomona, California*

In 1973, one of us (J.G.M.) was instructing a class of medical students on the vocational potential of people with disabilities. A gowned patient was wheeled in on a gurney and his condition presented as cerebral palsy, with speech impediment and severe ataxia. After the history and physical examination, the patient was wheeled out and the class was asked to make an appraisal of his capacity for learning or employment. The collective opinion was that the most he could do would be to sell pencils on the street. The patient got dressed, returned to the classroom, and this time he was introduced as Thomas Strax, MD, then Assistant Medical Director at Moss Rehabilitation Hospital, Philadelphia, Pennsylvania.

Given the present sophistication in emergency medical services and the field of rehabilitation, it is not surprising that more physicians are surviving accidents and illnesses or that an increasing number of people with congenital or childhood disabilities have strong early programming in favor of medicine as a vocation. But there are no reliable data indicating the prevalence of physicians with disabilities. An informal 1987 study found only 2.6% of all physicians and only 0.25% of currently enrolled medical students reporting disabilities, as opposed to 14.6% for the general population.[1] Another survey estimated there were 18,000 physicians in the country who were no longer practicing because of the onset of disability.[2]

Labeling has been a problem. Americans are understandably confused by the surfeit of designations, all seeking to avoid the use of stigmatizing labels. The only accord to be found among physicians is a universal distaste for the term "impaired physicians," which has come to be associated with substance abuse and mental conditions.[3] Given the lack of further consensus, Strax, now Medical Director of the Robert Wood Johnson Rehabilitation Institute (Princeton, New Jersey) and Chair of Clinical Rehabilitation at the University of Medicine and Dentistry of New Jersey (Newark), has proposed the following definitions: "Impairment is some particular trait that you're missing; it could be physical, mental, emotional, or whatever. A disability is something you can't do because of that trait. For example, if you have weakness in your right foot, then the disability is that you can't walk long distances. A handicap, on the other hand, has to do with function. So if you were a nighttime security guard or a patrol officer, you would be handicapped, but if you were CEO of Exxon, you wouldn't be. There are disabilities that are not handicaps, depending on the function that you put a person in."

It should be noted that the national organization of physicians with disabilities is called the American Society of Handicapped Physicians. "If they're handicapped," chides Strax, "then they have no business being physicians. Either you're excellent at what you're doing or you're not. So the concept of handicapped to me has no place [in medical practice]." Accordingly, this survey will focus on physicians with disabilities, not handicaps.

While the American Medical Association (AMA) has addressed the rehabilitation of physicians impaired by chemical dependency and emotional problems, vocational rehabilitation for physicians with physical or sensory disabilities is virtually nonexistent.[4] The American Society of Handicapped Physicians has attempted to prepare the ground for such an effort, but at this time most support and information still come from nonmedical sources.

The 18 physicians interviewed for this article represent a broad range of disorders: amyotrophic lateral sclerosis, spinal cord injury, deafness, blindness, postpolio weakness, spina bifida, cerebral palsy, and amputation. They divide into two groups whose life experiences differ: those who brought their disabilities to medical school with them and those who acquired their disabilities later in life.

Jessie Easton, MD, Chief of Rehabilitation Services at the Veterans Administration Medical Center and Clinical Associate Professor at the University of South Dakota in Sioux Falls, who had cerebral palsy and polio in her childhood years, offers this distinction gleaned from a blind friend: "To persons who are congenitally blind, being independent means being able to call on a car and driver whenever they want to go somewhere. To persons whose blindness came later, being independent means being able to drive the car themselves."

Of the two groups, those whose disabilities occurred early in life confronted more attitudinal and financial barriers, but their disabilities required less adjustment in adulthood; those whose disabilities occurred later had better resources, economically and professionally, but may have suffered more acutely from the radical changes that accompany the later occurrence of disability. All are actively practicing medicine, and most are in highly visible and responsible positions.

The choice of specialty was usually influenced by the disability if it occurred before or during medical school and concentrated in the areas of physical medicine, psychiatry, pathology, and anesthesiology. Those with a later onset tended to stay in their original specialties, taking advantage of their professional assets to adjust their work and their workplaces to accommodate their new needs. Wainapel has reported on the clustering of specialties practiced by physi-

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From the Casa Colina Hospital for Rehabilitative Medicine, Pomona, California (Dr Madorsky). Mr Corbet is a filmmaker and writer on disability-related issues. His book, *Options: Spinal Cord Injury and the Future*, AB Hirschfeld Press, Denver, Colo, 1980, is currently in its eighth printing. Mr Corbet became paraplegic after a helicopter crash in 1968.

Reprint requests to Julie G. Madorsky, MD, Casa Colina Hospital for Rehabilitative Medicine, 255 E Bonita Ave, Pomona, CA 91767.

ABBREVIATIONS USED IN TEXT

AMA = American Medical Association
EMG = electromyogram

cians with disabilities and adds internal medicine, family medicine, radiology, and pediatrics to the list.[5]

Adaptations

Adaptations to compensate for disabilities, in practice or in medical school, are increasingly creative. The most rapid change has occurred in adaptive devices: in addition to the familiar telephone relays and telecommunication devices for the deaf, recorders and braille signage for the blind, and durable products such as wheelchairs and motorized scooters for those with mobility impairments, technology now offers talking thermometers, vibrating beepers, optical-tactile converters, braille sphygmomanometers, braille transcription services, devices to scan and vocalize print, high-powered lenses with video display, computers and software operable by headset or by "sip and puff," and voice-activated telephones and environmental controls.[6] Audio digests and computers can be used to access data bases and to provide continuing education, and computers are on the threshold of adding many more solutions.

Not all adaptations require high technology. Serena Young, MD, an orthopedic surgeon who practices in Long Beach and serves on the clinical faculty of the University of California at Irvine, had polio as a child. She has developed her own protocol for scrubbing and gowning with crutches and braces. Frank Jirka, Jr, MD, a urologist and past president of the AMA who has a double below-the-knee amputation, modified the cut-and-burn pedals of a Bovie cutting and coagulating machine for his use with a couple of door stops. Selma Calmes, MD, Chief of Anesthesiology at Olive View Medical Center in Los Angeles County (California), limits her standing time during operations by using a periscope to keep track of surgical progress.

People are another source of adaptation, from "gofers" to drivers, interpreters, researchers, students, readers, note takers, and personal care attendants. Judith Pachciarz, MD, who has been deaf since early childhood, used the notes of other students to assimilate lectures at medical school and still uses a part-time interpreter in her practice. David Hartman, MD, totally blind since age 8, learned anatomy by touch and feels he learned it well.

David Rogers, MD, Medical Director of the Westside Regional Center in Culver City, California, is a geneticist and pediatrician whose quadriplegia occurred relatively recently. He has been particularly inventive in solving his mobility and dexterity problems: he uses a computer to access the world at large and a former patient with mild retardation and unbounded devotion to serve as his arms and legs by helping with telephone calls, transporting records, shuffling papers, stamping signatures, turning pages, and pushing the wheelchair.

Other physicians have called on partners to share or shift responsibilities to best use their capabilities, and the trend toward medical assistants is making delegation more feasible, if less affordable. Many find that they want, and have access to, a resident or other trained person for jointly seeing patients.

Environments can be modified psychologically and physically to compensate for changing abilities. Most physicians function best with staff familiar with their needs and routines, and a disability turns an amenity into a necessity. The workplace can be made accessible, clutter can be controlled, low lighting or noisy conditions can be rectified, and any of the devices mentioned can be integrated with the surroundings.

Discrimination

Discrimination is a fact of life for all people with disabilities, and, for those disabled early in life, prejudice has been encountered since childhood. Physiatrist Sharon Kawai, MD, Medical Director of Rehabilitation at Saint Jude Medical Center in Fullerton, California, who has spina bifida, was first treated as a child who would die soon, then later as a retarded child. She was turned down for kindergarten and again for grade school, but was eventually accepted by the latter on a two-week trial basis. Junior high schools initially turned her down but relented after a two-week probationary period. It was the same in high school: "I've spent all of my life on two-week probation." Her high school counselor hinted that it was futile to go to university at all, let alone to medical school; her state university medical school turned her down (no trial), so she went to another state for her medical school training.

Most disabled children were brought up to be brave and silent, reflecting an imperative to keep out of sight and out of mind. Kawai: "If something hurts, you just deny that it's there. Denial is such a big part of it. It's true that you have to keep on going, but it's not true that you have to deny your emotions. It was a hard transition from being a cute little crippled girl to achieving a measure of emotional maturity."

Strax, who has cerebral palsy, remembers a time when a disabled child was something to be ashamed of and hidden away. He was allowed to attend regular school classes, a first for the city of New York and due only to his parents' persistence in court, but not before he was exposed to bus drivers who did not want him on the bus and educators who felt he was ineducable. Like Kawai, he had to constantly prove himself: "My parents' attitude was that I should be able to exist in society, so they urged me to do everything I wanted to do to encourage me. And in the meantime they were putting away money to buy me a candy store."

Advisors were not always supportive. Pachciarz is a pathologist at H. Claude Hudson Comprehensive Health Center Laboratory in Los Angeles: "They didn't think it was possible at all. They'd say, 'You're deaf, you're a girl, and you want to be a doctor?'"

Almost omnipresent was the presumption of retardation, especially for those who are visibly or audibly different. Strax, somewhat gleefully: "Of course, of course. A lot of people think that somebody who has movement disorders is retarded or immoral. I'm immoral!" Pachciarz, less gleeful: "It happens every time I go into a store to buy something." Kawai: "Even today, people think that because you're in a wheelchair, you don't think as well as others." Richard Mailman, MD, an internist and faculty member at Northridge (California) Hospital Family Practice Residency Program, has amyotrophic lateral sclerosis that has recently affected his speech: "I don't know how people react to that. I know how I react to it. I hear my voice and it sounds so retarded, and then I start thinking that way."

While society at large struggles to come to grips with disability rights, it is not the only source of discrimination facing physicians or aspiring physicians with disabilities. Discrimination comes from within the medical profession. A constant refrain is that physicians, however educated and beneficent, are a steadfast impediment to bringing the disabled into medicine.[7]

Jyh-Hann Chang, a quadriplegic student who has applied unsuccessfully to many medical schools, feels that medicine has an opportunity to make a point: "People with a medical background generally understand that a physical disability doesn't affect mental ability. I think that, having that knowledge, they should understand that our abilities are unchanged."

Acceptance to medical school has presented enormous barriers to people with disabilities, and still does. Applicants run into technical standards that effectively bar all people with disabilities. Here is an example:

> Candidates for the MD degree must have somatic sensation and functional use of the senses of vision and hearing. . . . coordination of both gross and fine muscular movement, equilibrium, and functional use of the sense of touch and vision.[8]

Stanley Wainapel, MD, Associate Director of Rehabilitation Medicine at St Luke's-Roosevelt Hospital in New York, has choroideremia, a progressive visual impairment. He notes that technical standards contravene the affirmative language of section 504 of the Rehabilitation Act of 1973.[9] Of 127 medical schools in the country, 28 rely on technical standards and only 2 report a policy of not considering disability in the admissions process, so clearly prejudice is still present.[1] Pachciarz, who embarked on an epic 17-year quest to enter medical school, found that schools did not bother to hide the fact that she was being rejected for her deafness. For other disabilities, they seem to feel on less firm ground.

Jyh-Hann Chang: "Most schools [used] just basic rejection. A lot of them wouldn't state why I was rejected. Five came straight out and . . . said it was the disability, but they would never put that into writing. It came out after verbal requests. I would ask them if the disability was a factor, and they would say yes or no or that I was rejected on technical standards."

Margaret Stineman, MD, a physiatrist and Assistant Professor of Physical Medicine and Rehabilitation at the University of Pennsylvania, Philadelphia, who has multiple congenital malformations of the musculoskeletal system: "Some schools interviewed me because they were curious, because I was different, and some schools flatly rejected me. Either they had filled their 'quota' of disabled people or they just thought that I couldn't do it."

Hartman, a psychiatrist practicing in Roanoke, Virginia, feels his blindness took some getting used to from his peers: "At first there was some ambivalence in the field of medicine as to whether I could do a full evaluation or not. I didn't feel the people saw me as someone who would take responsibility."

Strax: "The dean at the time didn't think someone with a major disability like mine could possibly have the emotional adjustment to be at the New York University Medical School, and he opposed it."

Jirka, who did not himself experience prejudice, speaks from his viewpoint as a double amputee: "Whether they admit it or not, there is some resistance to permitting people with certain forms of disability to pursue their livelihood, that is, to go into medicine. I would certainly hope that it's strictly based on academic abilities and not on any physical disability, but I'm not sure that's always the case."

What selection committees most often founder on is the inaccurate perception of limitation. It is easy to wonder how people with disabilities can do specific tasks, and it is even easier to assume that they cannot. Pachciarz: "They just assumed that I couldn't do it. I would explain technical advances, I would bring pictures of my instruments, and I would explain how to do it. Even after I answered, they felt uncomfortable. They didn't want to say yes, but they had a hard time saying why not."

Wainapel thinks that the problem stems less from prejudice than from ignorance: "There's a great deal of unawareness from physicians, in admissions committees, and in many levels of the medical community, about what a person with a disability can accomplish. I don't think it's occurred to many of them that the white coat is a symbol that does not have to be worn standing up or that a physician does not have to be taller than the patient. It's important that people not have preconceived notions of limitations, of what cannot be done."

Some barriers seem totally frivolous. Young, an orthopedic surgeon: "The dean asked, How could I catch a baby? How could I run to a code? What does that have to do with orthopedic surgery? . . . I can't do orthopedics because I can't run down the hall? How can people get so ill-focused?"

The barriers sometimes extend to the workplace. Stanley Yarnell, MD, Director of Spinal Cord Injury Services at St Mary's Hospital, San Francisco, has recurrent optic neuritis and has been legally blind since 1978. He had been medical director at a different institution for three years, but things changed abruptly once his blindness advanced enough to require a white cane: "They said, 'Because of your vision, we think you're a medical-legal liability, and we don't want you to be medical director anymore.' I was numb. I thought, I'm so good at what I do, I couldn't believe that somebody wouldn't want to make an accommodation for me." The hospital worried that he might not be able to do certain procedures, then that he might not be able to deal with the emotional problems of newly disabled kids. "That's just wrong. If anything has happened since I started using the stick, it's that I am much more effective dealing with disabled people. People look at me, and they know I know what I'm talking about. And I think I'm a little more empathic, too, as all disabled people are with other disabled people.

"Then I proposed ways to accommodate the problems, but they fell upon deaf ears. The staff, rather than hearing what sort of problems I was having, just made up their minds about what the problems must be. Really, it was all from ignorance and prejudice."

Yarnell's adjustments in his private practice were relatively simple; handing off procedures such as electromyographies (EMGs) and nerve blocks to his partners and keeping a sighted resident at his side when seeing patients. St Mary's was entirely supportive, and his patients threw a surprise party for him. Yet scars remained: "I have a lot of self-confidence, but it was rocked to the core by [institutional prejudice] even more than adjusting to personal changes. I thought this was the beginning of the end. 'Did you hear that Yarnell is a medical-legal liability?'"

These events occurred to a physician who was successfully established in practice. For newcomers with disa-

bilities, negative attitudes can seem impenetrable. But established or otherwise, many encounter deep-seated devaluation.

Young described her first residency as "an environment of isolation," and it included a brief exclusion from the operating room. The lack of acceptance was not from patients or nursing staff, but from physicians. "You'd think that doctors would be the most open and accepting people. You're able to walk on braces and crutches because of their medical technology. It would seem that if this person could have a great life in spite of the disability, that it would show that medicine was accomplishing its goals."

Calmes, an anesthesiologist who has postpolio syndrome, feels she cannot bring her motorized scooter into the operating room because of the image it presents. "It puts me in a less powerful position. At the end of the day, I can hardly walk." And there are technical objections: "The first time I tried to use the scooter in the operating room, the head OR nurse felt that it was electrically unsafe. They actually called an electrician to look at it. I think she still believes that it's electrically hazardous."

Glenn Reynolds, MD, Medical Director of the Rehabilitation Center at St Joseph's Hospital, Tacoma, Washington, was disabled by polio while he was in medical school. "I learned even before I had polio that you can solve almost every problem, so the biomechanical aspects of disability have not been as profound for me as the psychosocial problems. There is a need to fight for every bit of territory to justify who you are and what you're doing. Over the years, the paternalism and patronization are the worst things that happen with a disability."

Only infrequently is the condescension funny: "When I went back to school in a wheelchair, one of the residents saw me on the ward and said, 'What are you doing down here? This place is for doctors and nurses. Why don't you go back to bed!'" Evidently, this is not an isolated occurrence. Strax: "I have people who ask me what room I'm in, so I give them a room number."

Pachciarz's story is atypical, yet it contains all the elements that describe medicine's reaction to people with disabilities. After being rejected by medical schools because of her deafness and speech—she has what she calls "deaf speech"—she took a detour and earned a PhD in microbiology. Her intention was to use that degree as a springboard into medical school, but eight years after earning her PhD, she still had not been accepted. Why? Several things needed to happen. The telecommunication device for the deaf was developed, interpreters became available, political awareness of disability issues grew, and section 504 of the Rehabilitation Act of 1973 began to be implemented.

What tipped the scales? "One factor was that I had gone to all the interviews without an interpreter. I depended on my speech, because I was programmed to believe that I could talk, that I could succeed in the hearing world. . . . There were people who were kind to me, too kind. They didn't just come out and tell me that my speech was not understandable by the general public. It takes a little time for a person to understand my speech, and for an interview, that's not good."

Pachciarz discovered interpreters in 1977 and used them in interviews thereafter: "Speech therapy never got me into medical school. Interpreters got me into medical school. After 17 years, we together that morning accomplished what had never been done before." She points out that her 17-year quest represents a 17-year lag in her life, 17 fewer years to develop a retirement plan, 17 fewer years to buy a house, and 17 years lost to medical services.

Pachciarz offers a particularly eloquent passage taken from her "Viewpoint of a Deaf Professional Woman,"[10] no less valid for all disabilities in its attention to deafness:

> Our success stories prove what we can do but don't give a true picture of the many who suffer discrimination as opposed to the few who are held up as examples. One response to those who succeed is to exempt them as being exceptional and unlike others. Thus, one by implication agrees with societally condoned assumptions about the deaf as a group. . . . so that we are stereotyped as a minority group by being expected to be grateful, patient, respectful, dependent. Such stereotyping in itself is crippling. That a few deaf have "made it" tends to obscure the fact that as a group we still suffer discrimination.

Female physicians with disabilities may face gender discrimination in addition to that occasioned by a disability. There are more and more women these days practicing more and more specialties, but hardly enough to rock the status quo. Medicine has always been a male-dominated profession, and it still is. Kawai: "When I decided to go into private practice, I was turned down by many rehab hospitals, and I was told quite frankly, 'You're a woman, and you're in a wheelchair.' So I think I have a double handicap in that sense." She notes that lower pay and slower advancement are still givens.

Asked if she had encountered prejudicial work situations, Young's response was flippant: "Yeah, but what else is new?" When pressed, she elaborates: "Orthopedics is a male-dominated specialty, and it's not only male-dominated, you've got to have a certain quality about you. It's really elite, and I don't fit the mold in any way, shape, or form. So I don't know whether the difficulty was because I'm female or because I have a disability. I know other female orthopedic surgeons who feel incredibly discriminated against because of their gender, so it's hard to sort that out."

Without minimizing the undeniable presence of prejudice, it should also be pointed out that all the physicians interviewed for this survey, male and female, embarked on medical careers because they admired physicians and the ideals they uphold, and all can recall instances of support and accommodation from their medical mentors. The surgeons on Kawai's surgery rotation gave her the money she needed for braces to enable her to stand in the operating room. The example, support, and influence of Howard Rusk, MD (one of the founding fathers of rehabilitation medicine), favorably affected the careers of Reynolds, Strax, and Hartman. Mailman has been able to stay in practice through the creative help of his colleagues. Easton remembers the orthopedic surgeon who suggested rehabilitation as an alternative field when she was disqualified for surgical training because of her disability. Rogers, with the most recent onset of disability, feels his associates have been unstintingly supportive.

Sometimes there are pleasant surprises. Young: "I know a hand surgeon who had polio that affected his hand. He didn't even tell me about it until one night when I had just started at the hospital, he asked, 'What are you doing on crutches?' He was laughing at me. So I said, 'Oh, I had polio.' And he says, 'You know, so did I!' And he showed me his hand."

Nor should it be assumed that medicine has not changed. The dean who had opposed Strax's admission to medical school caught up with him in a hallway years later and offered his apologies and congratulations. Once physicians with a

disability are seen as having an active and caring role in the profession, resistance vanishes and constructive change occurs. Similarly, once medical schools have accepted their first students with disabilities, they tend to keep on accepting.

Entire communities have sometimes provided overwhelming support. Donald Seanlon, MD, an internist at the Monterey (California) Peninsula Community Hospital, became quadriplegic in his early 50s. While he worked on his rehabilitation, his community worked on getting him back. Within days, his hospital had made personnel changes, found accessible office space, and created a new job for him. There was another job offer, this one from Reynolds, who was then running the Santa Clara (California) Rehabilitation Division. And a number of his colleagues volunteered their time to keep his office open. "That was an enormously uplifting experience, to find that outpouring of love and concern, so many people being so helpful. It's made the difference between really feeling wiped out and depressed and being able to adapt to this." How has the disability affected his practice? "It's meant I don't have to make night calls any more, so I'm adjusting very easily."

Compensation

Most physicians with disabilities who have gone beyond medical school into the day-to-day realities of clinical practice have found that the profession treats them well. Most do not feel an unfair loss in earning power, and several remark that their disabilities have made them stand out in ways that attract recognition. There are, however, hidden penalties that most people with disabilities experience.

The cost of maintaining a disability can make dents in a perfectly adequate salary. A lift-equipped van can cost more than $30,000; Mailman laments the $6,000 it costs to buy a powered wheelchair, and Pachciarz cites the $400-a-day cost of hiring an interpreter and the time expended to teach coworkers optimal communication strategies. Anyone with a vision loss has the need to hire cars and drivers, and many people with disabilities face problems buying life or health insurance. None, interestingly, reported any prejudicial rating in malpractice insurance. But time, more than any other factor, limits their earnings. Either tasks take longer to accomplish, or the disability itself demands hours of nonwork attention. In either case, the penalties are always the same—less leisure time, less compensation, and, likely, more stress. All of these physicians, with only one exception, described themselves as overachievers. What, then, does an overachiever do when obliged to spend a significant part of each day compensating for a disability?

Yarnell is a case in point: "I immersed myself in my work. One way of forgetting about myself was when I was fully focused on my patients. And I made a mistake that a lot of overachievers do, I forced myself to continue to carry the same workload. I'm much less efficient than I used to be. I would get behind, and then I would get angry with myself. I'd get impatient with the staff, and I realized it was becoming counterproductive . . . I saw that I needed to set limits on myself and [to] just say no." Wainapel: "This is a hard time for me. I'm aware of my assets, but I also have a lot of feelings of inadequacy that I'm struggling with now. I'm competent intellectually, but I have extra klutziness now because it's hard to get around. It annoys me that I can't find things, that my eyes get tired, so I do tend to get down on myself now. It's a lot of little things that add up, partly because of [the] image that the doctor should be able to do everything."

There is a tendency to deny dysfunction. At medical school, all who could do so concealed or minimized their disabilities, sometimes at major cost to their health. Some are still doing so. Often the problem is in meeting outside expectations. Stineman: "Either people think I'm inferior, or they think that I'm some superhuman person. They get this idea that, 'My God, if she can do this given all the problems, there must be something remarkable about her.' Both extremes are bad. If people see you as superhuman, when they find out you're just a human being, they're let down. And at the other extreme, of course, they don't give you a chance; they just close their minds."

The Compleat Physician

Medicine has long harbored an unwritten code of perfection, and physicians are often seen in unrealistically heroic terms.[11] So the label "disabled physician" may be a harsh oxymoron to some.

Calmes: "This idea of the perfect healer, the godlike person, just simply is unrealistic. The whole culture of medicine would improve if it were possible to consider the whole person, to capitalize on strengths, not weaknesses."

Yarnell thinks that able-bodied physicians need to acknowledge being human: "The medical-legal thing is easy to hang on to, but it's that old problem of the physician as deity, the doctor as God, and sometimes physicians start to believe that. We're all taught about it and cautioned about humility, but the truth is that physicians start to believe it."

The undefiled healer conceit is difficult to shake, sometimes even for physicians with disabilities. Yarnell remembers how stoutly he resisted attending a low-vision support group, something he eventually found helpful. "I had all sorts of excuses for not wanting to go at first, not the least of which was because I was a physician. Somehow, I was different."

From the image of the "compleat healer" arises one of the manufactured obstacles that physicians with disabilities often face, the notion that being visibly or audibly different will ruin the physician-patient relationship.

Patient Acceptance

Patient acceptance is a concern that weighs heavily, but only briefly, on most fledgling physicians with disabilities. Uniformly the finding has been that, in the face of disability, the physician-patient relationship holds up well. Yarnell: "My vision impairment is an annoyance, and I'm less efficient, but in terms of the way my patients . . . perceive me, there has never been a problem. I tell them I'm visually impaired, and they're very good about it. It's very matter of fact. It's how disabled people deal with other disabled people, not condescending, just a statement of fact. It hasn't been an issue with a single patient. Wainapel: "I'm capable of taking the metaphor of vision loss and applying it to other disabilities. I can't tell someone who's paraplegic that I know what it's like to be paraplegic, but I can say that I know what it's like to be stigmatized. The cane is a powerful symbol of empathy. You're a physician-patient. You know what it is to be on the other side, and if you have any degree of sensitivity, you know what it is to be afraid and you know what it is to be badly treated. At a time when there are calls from all sides in

the medical schools for teaching compassionate human care, a person who has a disability or who has been ill can provide that from a depth of self-knowledge that's not normally available."

Calmes works mainly in pediatric anesthesiology: "When I buzz in with my scooter, the kids love it. They follow me around the ward, so it's been a great attention getter for the kids. And it puts me at a child's level, so I'm not towering above them." Does she like the concept of the wounded healer? "I'm still trying to come to terms with that. We *are* supposed to be perfect."

Is the disability a help or a hindrance? Scanlon: "It's . . . a help in . . . relating to people, person to person. When you relate as a physician, . . . often there's a certain remoteness. It's easy to be detached or cold and for patients to regard you as not understanding. My situation is that they usually assume that I know what it's like to be a patient, and sometimes they act apologetic for their complaints compared to whatever they think mine are. To them, I've got real problems. There's a positive built-in arrangement between us that makes it much easier."

Easton: "If I tell them to wear a brace, they know that I know what a brace feels like. It helps with the patients, and it certainly helps with the parents of the handicapped kids that I understand."

Reynolds: "Disabled people's empathy in dealing with other people who are disabled is a great asset in this day and age when everything has been reduced to a procedure. There are so few people who get a chance to have someone sit down and listen to them and help them work out a problem, and any disabled person who's in medicine can do that. It's worth more than any dexterity of arms or legs."

But the blessings of a disability are not without limit. Hartman: "There are times when people who have just lost their sight come into the room and they're very intimidated. One reason is they somehow feel that they've been relegated to the blind group, and they feel uncomfortable. Or I come in, I'm independent, I seem to be able to get around pretty well, and they feel overwhelmed. They think, 'I can never get from where I am in bed to where that person is.' Another thing that I've learned is that in my enthusiasm, I'll come in and start talking to a patient about what they can do, and they say, 'I can't do anything, I'm blind. I won't be able to have a family.' So I say I'm married, I have kids, I live a happy life, I ski, I swim—well, they don't want to hear those things. What they want to do is talk about their losses. So over the years I've learned to keep my mouth shut." Yarnell: "I try not to dispel any myth that blind people have some extra sense. There's nothing to it, but if people want to believe it, I let them. I've been able to parlay this into a positive thing. It's not just me . . . anybody who's got a disability can relate better to others who have disabilities."

Strax is more cautious: "I feel strongly that understanding, humanistic people come in all shapes and colors, and I don't believe that because you are a woman you are a better gynecologist than a man, and I definitely don't believe that because you have a disability, you're a better physiatrist than if you were able-bodied. Sensitivity is a separate issue." On the other hand, "You're perceived as being warm, humanistic, and caring, as understanding how it really feels. You can always use that, and if you actually are, it's even better." How do his patients accept him? "People perceive confidence." Strax reports this scenario: "When I was at Temple University Hospital [Philadelphia, Pa], I had the privilege of being part of the training for David Hartman. I dragged David over to the rehab department, and we'd drop in to see patients. Can you imagine that? You're a patient lying in bed, and in comes your consultant with cerebral palsy and introduces his blind medical student!"

Advice for Medical Schools

All of these physicians would like to see medical schools become more receptive to students with disabilities, and they have some collective advice for schools and their admissions officers: See abilities, not disabilities; see individuals, not statistics; see whole persons, not impairments. Most of all, do not lower the standards of training.

Kawai: "In the interview process, try to eliminate any bias you might have. I think a lot of able-bodied people are terribly afraid of becoming disabled, just like we're all afraid of dying. [We] represent everybody's worst fears. Really think carefully—this is a whole person."

Pachciarz: "Don't assume anything. Ask specific questions about how an applicant will handle things. Don't make the mistake of assuming that because someone is missing something, they don't have the ability to do something. Just ask that person how they would accomplish it. For example, ask a deaf person, 'How would you evaluate heart and lung sounds?' That's a perfectly valid question. It's not acceptable *not* to ask that question. Ask how a person *could* do something."

Jyh-Hann Chang offers his perspective: "I have a lot more than just my disability, and it upsets me that some of the schools don't recognize that. I would like them to start viewing the benefits instead of only concentrating on what can't be done. They should concentrate on what that person can offer to the profession. If a candidate has gotten through the curriculum and is there for an interview, he probably isn't . . . a slouch. He's already proven something by the time he arrives."

Reynolds urges admissions officers to make use of advisory panels of select rehabilitation specialists to help them make better-informed decisions. Perhaps some of the specialists should be physicians with disabilities.

Rogers would like all medical students to have exposure to practicing physicians with disabilities: "That would open some eyes. . . . by admitting students with a personal medical background, you're going to develop a different kind of doctor. You'd have a much more realistic outlook."

Hartman: "We need to be careful not to be stamping out form-fitted physicians. I . . . teach . . . medical students, and I see a lot of competent, bright students. Rarely do I talk to anybody who has experienced much of the medical system. They're people who are healthy, have never had medical problems, and they really don't have strong feelings as consumers. It's exciting to think of ways that we can provide a more diverse group of clinicians to the field."

Will accommodating students with disabilities place a burden on the system? Hartman thinks not. "The system will benefit. . . . medical schools [will be] forced to discuss and exhibit materials to students in more creative ways. . . . You're going to see a more creative teacher."

Hartman thinks that a lot of confusion could be cleared away, both for new students and admissions officers, by understanding what physicians do: "Physicians are people who

gather data, put it together, and come up with diagnostic impressions and ways in which to treat clients."

Strax has another message: "What I would like to do is educate people that there's nothing shocking about people with disabilities in medical school. There's nothing that I've done that was that difficult. Medicine requires a very gross kind of handwork. It doesn't really take tremendous dexterity. It takes intelligence, and it takes knowing what you're doing, but that has nothing to do with physical attributes. I would like to desensationalize the issue, because I don't think there's anything tremendously sensational about it."

Advice for Physicians

How should physicians treat their peers with disabilities? Scanlon suggests that his own experience could serve as a model: "Physicians have the opportunity to be as thoughtful and supportive of their colleagues as my colleagues have been to me. I would urge them to recognize that sort of opportunity."

This affirmation notwithstanding, the medical edifice attracts some commentary about the way it does business. Several of these physicians wish their colleagues would respect the fact that fatigue is not a sign of incompetence. Kawai: "In competitive private practice, . . . you're looking at physicians who want strong, able-bodied partners who can work from 5 in the morning until 10 at night." Easton, whose postpolio weakness has sapped her energy, wishes she didn't have to apologize for declining to do numerous EMGs a day: "I get tired. Some of the docs don't understand that, and they don't understand that there's nothing urgent about most EMGs. I can't buy that attitude anymore because I have to put priorities on how I use my energy." She wonders why part-time work is so dishonored. "I'm not really sure whether this business of working all hours is just plain ego or a way to avoid [having] an adequate social life."

Wainapel amplifies: "There should be the possibility of time-sharing, and not just for people with disabilities. . . . [For] physicians who [are] mothers [who] want to have more time for child-rearing, it should be possible to work part-time." Stineman wonders if internships could be shared to make the physical drain less demanding for physicians with disabilities. Mailman, unable to practice full-time, is gratified that part-time practice has become feasible for him. He is impressed by the difficulty of reconciling the full schedule of a physician with the extra time that his disability demands.

Despite recent improvements in removing architectural barriers, more change is needed. Calmes still finds herself frustrated several times a day by fire doors that are too heavy to open from a scooter. Mailman notes that most hospital rooms do not allow enough space for a power wheelchair to turn around. But he chuckles as he remembers resenting all those handicapped parking spaces before he developed a need for them. Easton's medical school provided elevator access to classes, but she was often accompanied by cadavers in transit. Reynolds tells horror stories about a lack of accessibility at national professional conferences, including those of rehabilitation providers, and he proposes a solution: "If the AMA or the state medical associations or specialty societies would make it a rule never to have a meeting in a building that has any access difficulties or that present paternalistic or patronizing approaches to disabled people, the effective lobby of this professional group could go a long way toward opening the doors for the people with disabilities that they serve. . . . it's doable. . . . there would be economic pressure on people to change." Will the Americans With Disabilities Act of 1990[12] help? "Legislation is not enough. By the time the administrators have imposed their rules and guidelines and directives, they can negate a vast part of the benefit that was built into the legislation. Compliance is a real problem."

Concern is also voiced over any hint of limiting medical licenses to one or more specialty. Hartman knows of a student with a vision impairment who went through medical school and is now practicing: "There was some controversy about whether or not he was going to get a full license to practice medicine or whether they were going to give him a limited license saying that he could only practice psychiatry. . . . that is an area which we disabled would want to fight against. The reality is that every physician has, not a license to practice every form of medicine, but a license that acknowledges their judgment to decide what part of medicine thay can practice and what part they can't. . . . It's as ludicrous for a blind person to do surgery as it is for a dean of a medical school who's been an administrator for 30 years to go back and start doing psychiatric work. The license indicates that we have the knowledge and the judgment to make a decision on what we can and can't do. Any blind person who does not have the judgment to decide what he can and can't do certainly shouldn't get a license. But I would say that about any clinician."

Yarnell: "Limited medical licenses? . . . That's silly. You have to be approved for privileges by the medical staff of each hospital, and even if you were just doing private practice in a clinic or office, you are accountable to a board of medical quality assurance. So there are those safeguards. But when people tell you what you can do based only on a perceived impairment, it's enraging. If I know that I've got choices, it goes a long way toward defusing that anger. After all, medicine is basically a cognitive process."

Advice for Medical Students With Disabilities

Some of the advice offered for aspiring physicians with disabilities is sobering. Easton is characteristically pithy: "There's great rejoicing about the Americans With Disabilities Act. It's fine, but you still have to be able to do the job."

Strax: "One of the hardest things for someone with a disability to get straight is that nobody owes you anything, and no one's really interested in your problems except your parents or someone who loves you. It's your responsibility to make it. I think those are rules for life which are very hard to learn."

Stineman feels that a choice of specialty is crucial to success: "You need to figure out where your strength is. Successful people, whether disabled or able-bodied, . . . go for things they can do well."

Young: "It's got to be something you want more than anything else in the world. Anything! If you're willing to sacrifice anything, then I'd say, 'Go for it.' The important thing to remember is not to let anybody say you can't do it. You have to prove to yourself that you can't do it before you can come to that conclusion."

Reynolds: "You do have to be a bit assertive, but be diplomatic. It's a lot easier to catch flies with honey than with vinegar. . . . it behooves people with disabilities who are entering into these ventures to be sure that they have not just gotten on an emotional jag but [that] they have tried to solve

all of the problematic questions before they get to the interview, because they could be made to look . . . ridiculous if they don't." He also offers the following, after Winston Churchill: "Never give up! Never give up! Never give up! Never, never, never give up!"

Conclusions

For all people with disabilities, discrimination is slowly subsiding in the light of awareness generated by their greater visibility in society, and this light shines on physicians and aspiring physicians with disabilities as well. Their growing presence in so many of the medical specialties has made the way easier by far. A comparison could be drawn with the four-minute mile—once Roger Bannister proved it was functionally possible, many others were able to follow.

Like Bannister, today's physicians with disabilities are pioneers. They have made it feasible to speak of disability as a useful stigma and the patient-physician as more than just an educated survivor. In the best sense of the phrase, physicians with disabilities represent business as usual in the long tradition of American medicine.

Medical schools can now build on their successful experience with students who have disabilities. Perhaps "technical standards" will no longer eliminate qualified applicants, perhaps the presumption of limitation will no longer be a first response to those who seem different, and perhaps medicine can rightly take pride in making constructive change possible. Perhaps hospitals, schools, and offices can continue to become truly accessible to all people, perhaps the world at large can do as well with its barriers, both attitudinal and architectural, and perhaps more students will come forward to accept the challenge of practicing medicine with a disability.

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ALARUM

I issue a call,
To those who cannot breathe or move
or hear or speak or see
As the world would have them.
Phoenix be!
From the ashes rise,
And meet the world
with defiance;
For struggle is victory!

ALBERT ANDERSON, MD©
Bronx, New York

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Americans With Disabilities Act of 1990
Implications for the Medical Field

MARILYN GOLDEN, *Berkeley, California*

The Americans With Disabilities Act of 1990 (Public Law No. 101-336, Statute 104, p 327; ADA) is a landmark federal civil rights law that protects disabled persons from discrimination in employment, transportation, public accommodations, telecommunications, and the activities of state and local government. I will summarize the act's chief requirements that affect the medical field. Those wishing further detail should contact my organization* or the Senate Subcommittee on Disability Policy.†

Defining Disability

The ADA defines disability broadly:

- A physical or mental impairment that substantially limits one or more of the major life activities;
- A record of such an impairment; or
- Being regarded as having such impairment.

Medical Facilities Are Considered Public Accommodations

The ADA prohibits discrimination in public accommodations. "Public accommodations" covers virtually all facilities open to the public, including hospitals, clinics, and physicians' offices—even when the office is in a physician's home—as well as other professional offices, restaurants, hotels, stores, and so forth. Most of the requirements for public accommodations go into effect on January 26, 1992. For public accommodations with 25 or fewer employees and earning gross receipts of $1 million or less annually, six extra months are allowed. For those that employ ten or fewer employees and have annual gross receipts of $500,000 or less, an additional year is allowed.

The ADA includes a carefully crafted set of general prohibitions on discrimination by public accommodations. First of all, a public accommodation may not discriminate against a person with a disability in the furnishing of goods or services. This does not mean that physicians must serve disabled patients outside their areas of specialty, but it does mean that they must serve a disabled patient if they would serve a similar patient without a disability.

It will be illegal to have a policy, practice, or procedure that has the effect of discriminating against a disabled person or a class of disabled persons, unless the public accommodation can show that modifying the policy or practice would fundamentally alter the nature of the goods and services offered. For example, it would be illegal for a pharmacy that accepts checks in payment for merchandise to accept only a driver's license as identification, because this would discriminate against some classes of disabled persons who are unable to obtain driver's licenses. A "no pets" rule in a pharmacy must make an exception for service animals such as guide dogs.

It also will be illegal to force disabled persons to participate in a separate or special program if they prefer to participate in a general program. If a hospital offers community health education classes, and it chooses to offer a special class for vision-impaired persons, it may not prevent a vision-impaired person from taking a regular class.

It is also illegal to discriminate against persons because of their association with a disabled person. A clinic cannot refuse to serve a relative of a person who has the acquired immunodeficiency syndrome solely because of that relationship.

Public accommodations must provide auxiliary aids and services, such as braille, amplifiers, and readers, if it would not fundamentally alter the nature of the service or pose an undue burden. For example, physicians will have to provide a sign-language interpreter to assist with communication during a medical appointment with a deaf patient, unless they can show that it would be an undue hardship. Hospitals also must provide such interpreters, as well as ensuring that a telephone display device, which is used by many deaf persons to conduct conversations by telephone, is available. If the hospital distributes written procedures on discharge to certain patients, it must provide those procedures, on request, in alternative formats such as braille or large print, for people with vision impairments.

The ADA also has architectural barrier removal requirements. Existing facilities are under the modest requirement that barriers must be removed when doing so is readily achievable. "Readily achievable" is defined as easily accomplished and able to be carried out without much difficulty or expense. This is a deliberately flexible standard that requires more of larger facilities than smaller ones. A large hospital would be required to do more than a physician in solo practice. For many facilities, this will require building small- or medium-sized ramps, adding grab bars, rearranging restroom stall dividers, adding a handrail to stairs, and other modest and affordable measures.

Where removing architectural barriers is not readily achievable, the operator of a public accommodation is still required to serve disabled persons through alternative meth-

*The Disability Rights Education and Defense Fund, (415) 644-2555, 2212 Sixth St, Berkeley, California 94710

†The Senate Subcommittee on Disability Policy, (202) 224-6265, 113 New Senate Office Bldg, Washington, DC 20510.

(Golden M. Americans With Disabilities Act of 1990—Implications for the medical field, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:522-524)

From the Disability Rights Education and Defense Fund, Berkeley, California.

Reprints not available

ods, if these methods are readily achievable. For example, if a pharmacy has five steps and a ramp of this size would not be readily achievable, staff must bring wheelchair users' prescriptions to them at the bottom of the steps.

More stringent requirements are placed on new buildings and buildings undergoing alterations, and they affect a broader scope of buildings than public accommodations: all commercial facilities are covered, including any facility where employment occurs. This broader classification includes offices that do not serve the public, as well as warehouses or factories.

New buildings have to be completely accessible to persons with disabilities. This covers buildings that are first occupied 30 months or more after the ADA's enactment date. When existing buildings are undergoing alterations, the altered area must be made accessible. Also, an accessible path of travel must be provided to the altered area if the area represents a primary function of the facility, such as the waiting room or examination room. Restrooms, telephones, and drinking fountains serving the altered area must be made accessible if doing these things is not disproportionate in cost and scope to the overall alteration cost. These architectural accessibility requirements include employee areas.

One exception to these rules in alterations and new construction is that in buildings under three stories or less than 280 m^2 (3,000 sq ft) per story, elevators are not required unless the facility is a health care facility or shopping center.

Who Is Responsible?

The prohibition against discrimination by public accommodations applies to any person who owns, leases (or leases to), or operates a place of public accommodation. Therefore, the owner of the building that houses a public accommodation, as well as the owner or operator of the public accommodation itself, has obligations under the ADA. If an office building contains a physician's office, both the owner of the building and the physician are required to make readily achievable improvements. Physicians make the changes to their offices and examination rooms, while the owner makes the changes to the primary entrance of the building and other general and common use areas, unless lease agreements otherwise allocate the burden between the owner and lessee.

Similarly, a door attendant or guard of an office building containing public accommodations would be required, if requested, to escort a person who is blind to the elevator or to write a note to a person who is deaf regarding the floor number of a particular office. The tenant is solely responsible for aids required in the leased space.

The owner of a public accommodation is liable for discriminatory policies. If a corporation that is building a series of clinics designs them to contain architectural barriers, an injunction could be brought against the corporation to enjoin the inaccessible new construction.

Employment

The ADA's employment requirements become effective on July 26, 1992, for employers with 25 employees or more. Employees are persons who are employed for each working day in each of 20 or more calendar weeks in the current or preceding calendar year. Two years later, on July 26, 1994, all employers with 15 employees or more will be covered. Employers with fewer than 15 employees are not covered by the ADA for their employment practices, although if they are public accommodations, they are covered by the sections of the ADA described previously, with responsibilities to their patients.

The ADA prohibits discrimination against any qualified person with a disability because of that disability, in regard to job application procedures, hiring and discharge, compensation, advancement, job training, and other terms, conditions, or privileges of employment.

Qualified Person With a Disability

The ADA defines "qualified person with a disability" as one who, with or without reasonable accommodation, can do the essential functions of a job. "Essential functions" means job tasks that are fundamental and not marginal. For example, many job descriptions list a driver's license as a requirement even though the job entails no driving. In these cases, having a driver's license would not be considered an essential function of the job. In determining the essential functions of a job, courts will give consideration to an employer's judgment.

An employer is free to select a qualified applicant and is under no obligation to prefer applicants with disabilities over other applicants. If, however, two applicants are equally qualified, an employer may not select the nondisabled applicant solely because of the other applicant's disability, even if the disability means the employer would have to provide some kind of accommodation.

Reasonable Accommodation

One of the ADA's most important requirements is that employers must make reasonable accommodations to the known physical or mental limitations of a qualified applicant or employee with a disability, unless the employer can show that the accommodation would impose an undue hardship. Accommodations can take many different forms. Making architectural changes to render facilities wheelchair-accessible; restructuring jobs; designing part-time or modified work schedules; reassigning to a vacant position; the acquisition or modification of equipment or devices; adjustment or modification of examinations, training materials, and policies; and providing readers, interpreters, or attendants are typical examples.

It is important to note that many persons with disabilities do not require any accommodation whatsoever.

The responsibility of an employer to accommodate an employee is limited to those accommodations that pose no undue hardship. Undue hardship means an action requiring substantial difficulty or expense; one that is unduly costly, extensive, substantial, disruptive, or that will fundamentally alter the nature of a business or program.

In determining whether a particular accommodation would impose an undue hardship, factors to be considered include

- The overall size of the covered entity, including number of employees, number and type of facilities, and size of budget;
- The type of operation maintained by the covered entity, including the composition and structure of its work force; and
- The nature and cost of the accommodation.

The requirement for reasonable accommodation is a deliberately flexible standard to incorporate the situations of employers of vastly differing sizes and means. What will be

reasonable for one situation will not be for another. Each situation must be evaluated on its own facts and merits.

Medical Examinations and Inquiries

In the past, employment application forms and interviews contained questions concerning applicants' physical and mental condition. This information often has been used to exclude applicants with disabilities, particularly hidden disabilities like epilepsy, diabetes mellitus, emotional illness, heart disease, and cancer.

To eliminate these discriminatory practices and assure that misconceptions do not bias the selection process, the ADA prohibits any identification of a disability by inquiry or examination before an applicant has received a conditional offer of the job. Employers may ask questions that relate to an applicant's ability to do job-related functions but not whether they have a disability. For example, employers may ask applicants for a typing job if they can type at a certain speed but may not ask if they have a disability. Any test may be given if the skills required to do the test are actually needed on the job.

Medical examinations may be conducted if they are given after a conditional offer of employment has been made, if they are given to all entering employees in a particular category, if the results are kept confidential, and if the results are not used to discriminate against persons with disabilities. This rule meets the employer's need to discover job-related disabilities.

Direct Threat

The ADA provides that if persons pose a direct threat to the health and safety of others, they are not covered by the ADA's protections and may be excluded from a job or a public accommodation. "Direct threat" means a substantial risk to the health or safety of others that cannot be eliminated by reasonable accommodation. The determination that a person with a disability poses a safety threat must be made on a case-by-case basis and must be based on facts rather than generalizations, speculation, irrational fears, or patronizing attitudes or myths about disabilities.

The ADA is of inestimable importance to millions of disabled Americans, and the disability community looks to the nation's physicians and health care providers to assist in its thorough implementation.

STAIRS

Instantly say I am unwanted.
Stairs.
Something is happening above.
Party or lecture.
A table laden with food
A great hall rowed with chairs.
Stairs.
Would destroy my plans; my dreams.
I would die were this to come to pass.
Stairs.

ALBERT ANDERSON, MD©
Bronx, New York

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The Sports Medicine Approach to Occupational Low Back Pain

GERALD P. KEANE, MD, *and* JEFFREY A. SAAL, MD, *Daly City, California*

Absenteeism caused by low back pain costs industry millions of dollars per year. Innovative approaches for the prevention and treatment of low back pain in workers are mandatory. The sports medicine approach for aggressive rehabilitation offers a possible solution.

(Keane GP, Saal JA: The sports medicine approach to occupational low back pain, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:525-527)

Many preconceptions confound the treatment of injured workers. Patients with injured backs are often viewed as complainers or malingerers. In addition, they may be regarded as unmotivated, unreliable, or even committed to agendas other than recovery. Copious data exist supporting the notion that patients with occupational injuries take longer to return to work and have less satisfactory recoveries than others.[1,2] These data contrast with those of injured athletes, who are highly motivated to recover and return to their professional activities quickly. The success achieved in athletic rehabilitation may serve as a template for designing new approaches for injured workers.

The passive nature of most treatment methods is a major obstacle to the recovery of injured patients with low back pain. Many of the time-honored mainstays of treatment, such as braces, soft tissue and pain modalities, manipulation, medications, bed rest, and even surgical intervention, are passive. Active patient participation has not been encouraged. Passive treatment fosters patient dependency, decreases motivation, and promotes a sense of helplessness. This passive treatment is in contrast to that of injured athletes, for whom an early return to action is the goal. Athletes are never treated simply with rest, pain killers, and bracing. Rather, they are immediately given an active program to preserve their joint range of motion, soft tissue flexibility, and muscular strength. Part of the solution in caring for injured workers is to offer them this kind of active, goal-oriented treatment. A selective use of passive methods may be beneficial but only as an adjunct to active patient-participatory treatment.

The basic tenets of athletic rehabilitation are early intervention, accurate diagnosis, timely and goal-oriented treatment, and the team approach. The team approach requires communication among the physician, physical therapist, and team trainer, with the common goal of a timely return to action for the injured athlete. These methods are now applicable to patients with occupational low back pain. Mayer and associates in a two-year prospective study that examined an active functional restoration program for chronically disabled workers demonstrated an 89% return-to-work rate as opposed to a 41% return rate in their nontreatment group.[3]

Testing

An important goal of functional assessment is to establish a data base to project treatment approaches and results. Measuring lumbar function is a major area of research among those studying the sports medicine approach to low back care. Studies currently under way examine methods that determine function, progress, and treatment results. Traditional methods that rely on the subjective reporting of pain as a measure are becoming less accepted. Traditional and modern testing methods should merge to provide a complete and reliable test battery. The improved and uniformly accepted methods for evaluating lumbar range of motion, lifting capability, and patient effort demonstrate the effects of rehabilitation.[3-5] For example, testing for isometric strength has been shown to have a significant correlation with the risk of work injury[6]; the progressive isoinertial lifting evaluation (PILE) recently developed by Mayer and associates uses real-life tasks in assessing lumbar functional capability.[6,7]

All objective means of assessing lumbar function should be used.[8,9] Observation of the patient and the use of inexpensive objective measures such as strain gauges and boxes with variable loads can provide good information about functional capability and determine the need for further evaluation or referral. Many clinicians are unfamiliar with the new, complex, expensive testing devices that assess lumbar function. Two attractive features of these devices include accurate graphics and reproducibility. These devices still may not measure patient motivation, however.[10]

In athletic rehabilitation, strength and range of motion are analyzed to determine when athletes can return to their professional activities. This approach can be adopted for the treatment of patients with occupational low back pain. The measurement of lumbar function, however, lacks the extensive data available for peripheral joints. Even seemingly simple variables such as range-of-motion measurements remain controversial.[5] Research is necessary to develop standards for lumbar function so that a reliance on subjective reporting will not be needed. Return-to-work criteria including lifting capability and standing and sitting tolerances are often best determined after an objective functional assessment.[9]

From the San Francisco Spine Institute at Seton Medical Center, Daly City, California.
Reprint requests to Gerald P. Keane, MD, San Francisco Spine Institute, 1850 Sullivan Ave, Suite 140, Daly City, CA 94015.

Treatment

Passive treatment methods have come under attack. For example, studies in recent years fail to support the use of bed rest for the treatment of low back pain. Deyo and co-workers found no long-term advantage to bed rest beyond two days for patients with acute low back pain.[11] In fact, prolonged rest promotes a substantial loss of bone mass, muscle mass, and possibly as much as 20% of strength level per week.[12-14] On the other hand, patient activity prevents the effects of rapid deconditioning and the frustration associated with prolonged rest and debility. Movement enhances disc nutrition[15] and ligament and tendon strength.[16,17] Patient education, a judicious use of anti-inflammatory medications, and adjunctive modalities such as transcutaneous nerve stimulation promote early patient mobility. Patients with persistent radicular pain often benefit from epidural or cortisone injections. More advanced selective nerve injection procedures may also be used.

Treatment must include patient education. Patients should be given information about the diagnosis, proper body mechanics, techniques of self-management and pain control, and ergonomic advice. Many patients find immediate relief from simple methods for lumbar positioning and exercises, such as MacKenzie press-ups or extension exercises.[18] Some advocates of postural positioning, however, tend to insist on flexion or extension exercises for all patients. In contrast, a recent approach, dynamic lumbar muscular stabilization, stresses the alignment of the spine, pelvis, and hip complex into a spine neutral position. A neutral position is defined as that position of spinal alignment in which individual patients find their own most pain-free state. Increasing abdominal muscle strength and using abdominal muscle bracing are important factors.[19] Patient satisfaction and compliance are high; progress can be swift and less painful. Patients are treated like injured athletes with improved self-esteem and a sense of involvement in the action-oriented treatment plan. By contrast, prescribing extension exercises for patients with spinal stenosis or spondylolisthesis, or flexion (Williams) exercises for patients with an acute anular tear only results in increased pain and frustration for them. Blanket prescriptions of extension or flexion exercises fail to account for differences in injuries.

Prescribing nonspecific "low back exercises" for an injured worker is as inappropriate as prescribing "leg exercises" for an injured football player. Once patients progress from the early phase of acute pain, a specific, active program of physical rehabilitation should begin. Support for this vigorous approach continues to grow with its use applied to all patients except those with progressive neurologic loss. A randomized study comparing the use of intensive exercise with lower intensity exercise and passive modalities by Manniche and associates found a significantly better outcome in terms of pain and disability levels in the intensive exercise group. Nearly 75% of the intensive exercise group versus about 20% of the most passive treatment group fell in the acceptable range of treatment response.[20] Exercise begun early, under proper supervision, and with adherence to good technique can safely and effectively relieve pain in patients with lumbar disc herniations and associated radiculopathies. A study by Saal and Saal evaluating the nonoperative approach to treating lumbar disc herniations through aggressive rehabilitation found a 96% success rate overall.[2] The speed of improvement and overall success rate are equal to or better than those in surgical studies.[21,22]

Developing an aggressive rehabilitation program, however, depends on an accurate diagnosis. Patients who fail to progress according to predetermined time goals should be reevaluated. Additional diagnostic studies may include magnetic resonance imaging or computed tomographic scans, electrodiagnostic tests such as electromyography or somatosensory evoked potentials, and other selective injection procedures.[23]

Improved overall fitness and aerobic conditioning are also important factors in managing and preventing back pain. Cady and co-workers found a strong correlation between levels of fitness and low back injury in firefighters.[24] The most physically fit persons had a considerably lower risk of low back injury. Worker's compensation costs decreased about 25% while employees were enrolled in the study's active health and fitness program.[24] Injured workers, like recovering athletes, must not only get stronger but must become aerobically fit to return to activity. This often involves major changes of life-style and education about cardiovascular risk factors such as diet and smoking. Exercise regimens that include walking or swimming and other light, nonimpact activities initially work best for back patients. Even the most pain-limited patient can do simple exercises such as pool walking and easy-paced swimming. Patients unable to do these nonimpact regimens require careful reassessment to find appropriate exercise levels.

Flexibility training for the hips and lower extremities is also an important feature of an active back rehabilitation program. Patients with injured backs, like athletes, need to maintain flexible lower extremity range of motion to reduce lumbar spinal stress.[25] A patient with tight hip flexors or hamstrings cannot develop the spinal positioning required to reduce lumbar mechanical demands.[26]

Many patients with back symptoms describe definite relief after completing their daily stretching programs, which consist of proper stretching techniques designed specifically for patients with low back pain. Warm-up and cool-down phases before and after exercise—the sports medicine approach—provide an ideal time to do flexibility routines. Industry has introduced programs designed to prevent back injuries by starting work shifts with warm-up stretching exercises. Promoting general fitness to prevent back injury needs further study but holds real promise.*

The key to treating injured workers is making increased function, rather than reduced symptoms, the treatment goal. The shift to active intervention that emphasizes an objective assessment of function and increased patient responsibility for recovery is here to stay. Physical reconditioning, strengthening, stabilization training, and a greater reliance on patient education and self-management may improve back care in occupational settings. The recent awareness of cost containment has encouraged these new approaches. Improved health care delivery to patients in the workplace, scientific and economic validation, and better communication between health professionals and industry are three factors that will contribute to a promising future for the treatment of patients with occupational low back pain.

*See A. J. Haig, S. Penha, "Worker Rehabilitation Programs—Separating Fact From Fiction," on pp 528-531 of this issue. Haig and Penha describe functional restoration programs for workers who do not respond to this sports medicine approach.

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Lifelessness is what scares me, not death.

Robyn Olson

Worker Rehabilitation Programs
Separating Fact From Fiction

ANDREW J. HAIG, MD, *and* SUZANNE PENHA, RN, MSN, *Neenah, Wisconsin*

A few worker rehabilitation programs have had outstanding success in improving ability to function for persons with occupational back pain. Local programs must show that they have similar success. Because the definitions of terms such as "back school," "work hardening," and "functional restoration" are blurred at a local level, the choice of a program for an individual patient must depend primarily on the program's demonstrated success rate with similar patients. The chances of returning to work decrease as a function of time after injury. Therefore, referring physicians, insurers, and employers must be provided with information regarding results in terms of acute (0 to 6 weeks), subacute (7 to 12 weeks), and chronic (more than 12 weeks) back pain. Other important variables include selection criteria, program cost, and dropout rate. We advocate standardized reporting of such data for all worker rehabilitation programs. A model "report to consumers," described here, is a minimal obligation. The validity of a number of important internal quality assurance issues is uncertain. Ethical and legal pressures must be recognized.

(Haig AJ, Penha S: Worker rehabilitation programs—Separating fact from fiction, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:528-531)

Good news for back pain sufferers! Researchers have confirmed that acute low back pain disappears regardless of treatment 95% of the time.[1] Only a small number require surgical treatment.[1] Thanks to a "sports medicine" approach to rehabilitating injured workers,[2] eight of ten patients with chronic back pain can return to successful employment.[3,4]

So much for pipe dreams. Although excellent studies have shown these results, we all know that back pain is the most common cause of disability in the working-age population.[5] The number of back-disabled persons is growing at an exponential rate. In fact, back pain costs this country tens of billions of dollars per year.

Good research and bad results may be partly due to a difference in quality of rehabilitation. The good results are primarily from university-based groups dedicated to back pain. In contrast, treatment is much more difficult for community-based physicians who have limited access to expert systems of case management and rehabilitation. We do have local programs with names such as "back school," "work hardening," and "functional restoration," but it is difficult to judge the quality of these programs. Are these programs appropriate for a particular patient? Are they successful? Cost-effective? Ethical?

In this article we aim to provide referring physicians, employers, insurers, and others the tools they need to assess the quality of care given to their patients. We begin with a description of the different programs, then address program selection, outcome measures, internal issues, and ethical controversies.

Worker Rehabilitation Programs

Worker rehabilitation begins with the first interaction with the medical system. An acute care physician is the first line of defense against disability. Because 80% to 90% of patients have no anatomically verifiable lesion and most patients improve regardless of the treatment given,[1] the physician's role in encouraging an early return to work is at least as important as "diagnose-treat-cure." We have shown that physician care consisting of urging patient participation in rehabilitation, an early assessment of medical and psychosocial causes for delayed recovery, and effective communication between the physician and the employer resulted in a substantial decrease of time away from work after acute injury.[6] Others have shown that early mobilization in a family practice setting may be more effective than some other treatment methods.[7]

On the other hand, there comes a point when a formal rehabilitation program is more successful than an individual physician's efforts. Studies comparing worker rehabilitation programs with care in the community[3,4] or even with care by the same specialist physician without the program[8] show the inadequacy of physicians alone. Clearly physicians must define an end point beyond which their resources are not likely to be effective. The Quebec Task Force on Spinal Disorders, which extensively reviewed the literature on low back pain, recommends consultation with a specialist before the seventh week after injury if a patient has not returned to work.[9]

The "back school" concept was developed in Sweden to consist of four 45-minute group sessions that educate patients on anatomy, pathology, prevention, and working in pain-free postures.[10] One randomized study showed that the Swedish Back School was more effective than placebo in terms of days missed from work over the year following the treatment of acute back pain.[11]

"Work hardening" has been defined rather precisely by the Committee on Accreditation of Rehabilitation Facilities.[11] Work-hardening programs "use conditioning tasks that are graded to progressively improve the biomechanical,

From the Department of Physical Medicine and Rehabilitation, Medical College of Wisconsin, Milwaukee (Dr Haig), and the Center for Rehabilitation Services at Theda Clark Regional Medical Center, Neenah, Wisconsin (Dr Haig and Ms Penha).

Reprint requests to Andrew J. Haig, MD, Medical Director, Center for Rehabilitation Services at Theda Clark Regional Medical Center, 130 Second St, Neenah, WI 54956.

neuromuscular, cardiovascular, metabolic, and psychosocial fitness of the individual with real or simulated work activities."[12(p69)] The concepts are explained by Matheson and co-workers, who popularized these techniques.[13] Although dozens of "how to" articles have been written on work hardening, little had been done to document its success until recently.[8,14] Work hardening has generally been accepted as a reasonable treatment for some people with occupational back pain.

One of the most exciting advances in the rehabilitation of persons with back pain is the finding[3] and independent confirmation[4] that 80% of persons with work-disabling chronic low back pain can return to meaningful work through a complex, intensive, interdisciplinary rehabilitation program based on the quantification and improvement of measurable functional variables. Only 40% of persons without this care returned to work. These are called "functional restoration" programs.

Problems in Execution

If a local program replicates all elements of one of these three types of programs, it may be successful. We cannot realistically assume that programs are photocopies, however. Programs disregard formal definitions. They add or subtract from the format because of local resources or philosophy. They change the format in an attempt to improve outcome or reduce costs.

Definitions have been confused. The most recent review of back schools[15] shows that the term "back school" has been used for programs ranging from two lectures to a six-week inpatient hospital stay. Most of the programs that were significantly different from the Swedish Back School were not carefully studied against a control group. Their effectiveness cannot be judged. Local programs may change their names without changing the format to improve reimbursement.

Local resources may differ. There is a trend for some employers to provide work-hardening activities at the work site. A competent pain psychologist or vocational counselor may not be available. The program may need to share space and staff with an inpatient therapy department.

Differing philosophies may result in different executions. Although pain and function do not always correlate,[2] local physicians and therapists may "back off" therapy intensity to varying degrees when pain behavior is present. Therapists may take an adversarial, supervisory, or collegial approach to patient interaction. When quantifying function, programs may not measure true maximum performance or may use expensive high-technology machinery to document improvement in areas that have no clinical relevance.

The approach to psychological versus physical rehabilitation for work-related back pain is a hot topic. Studies have shown that patients with back pain are physically deconditioned[3,4,16] and that strength below job requirements predisposed them to injury.[17,18] Similarly, psychological and vocational behavior are important.[13,19] A randomized study showed that both a purely psychological and a purely physical approach resulted in equal success in returning patients to work.[20] Sachs and co-workers report that their primarily physical "work tolerance" rehabilitation program is as effective as a multifaceted "functional restoration" approach to chronic disability.[8] Elsewhere a low-intensity, less expensive, functional restoration approach is being used for persons with acute or subacute pain.

Program formats may change in an effort to improve results. For example, the functional restoration program Productive Rehabilitation Institute of Dallas for Ergonomics (PRIDE) recently published improved results with the addition of preprogram training and education.[21] Other program elements need further study. How important is job simulation versus a generalized reconditioning approach? Does alcohol and drug treatment affect outcome? Do any of these approaches prevent reinjury?

Back school, work hardening, and functional restoration have been well defined by the researchers who worked out and validated these concepts. In practice, these programs have been confused and intermingled for a number of reasons both good and questionable. Although the Committee on the Accreditation of Rehabilitation Facilities and the American Occupational Therapy Association have provided helpful guidelines for some types of worker rehabilitation programs,[12,22] the quality of a local program cannot reliably be judged by its adherence to rules. Proven results are the best indicator of future success.

Selecting the Right Program

A referring physician's responsibility is to refer patients to the right program at the right time. A program's obligation is to delineate its approach and appropriately screen patients for admission. While back pain progresses along a continuum from acute to chronic, rehabilitation is often separated into discrete steps. It is useful to base the decision to advance to the next step on the cost-effectiveness of the treatment.

Because the cost of an episode of acute back pain is minimal, an inexpensive back school is reasonable. Patients whose acute back pain is likely to become chronic must be identified[5] and referred to a more aggressive approach that may be cost-effective.

The care of patients with subacute back pain has been somewhat more costly. Chronic pain is likely to develop in these patients without intervention. A work-hardening approach may be effective. Even more cost-effective may be a return to work on a gradual basis if a patient is physically and emotionally able to meet job demands. Work hardening may be ineffective in persons who are headed towards surgical treatment. Patients with many psychosocial issues usually need more than a simple physical conditioning approach.

Patients with chronic back pain make up only 5% of back pain sufferers, yet they account for 85% of cost.[1] If no medical or surgical cure is found, a functional restoration program may be indicated. Back school alone has been proved ineffective in this group.[23] A work-hardening program that accepts patients who have chronic pain must demonstrate its effectiveness in this group separate from its subacute pain patients.

The wishes of patients who decline to participate in an appropriate program should be respected. Unless the circumstances can be altered, active medical intervention should be ended and referral to a vocational counselor considered.

Measures of Outcome: All That Really Matters

A sophisticated approach must be used when evaluating the effectiveness of individual worker rehabilitation programs. For example, a 70% return-to-work rate for patients with chronic low back pain may be excellent, but the same percentage for acutely injured patients is worse than the natural history of the disease. In the model "report to con-

sumers" (Figure 1), we provide guidelines that even the simplest program should be able to meet. More comprehensive approaches to proof of effectiveness are provided by others.[24]

Basic information on the program should include cost, number of days the program is designed to last, number of hours per day, and qualifications of the program staff. Persons with problems other than back pain should be excluded from all calculations. If one organization has two different programs (a back school and a work-hardening program, for instance), results should be described separately.

Program variables must be separated according to the length of the time patients are disabled on admission. The Quebec review suggests a protocol in which patients are divided into those whose pain has been present 0 to 6 weeks, 7 to 12 weeks, or more than 12 weeks.[8]

Patient demographics should include the number of men and women, age (mean and standard deviation), and percentage with previous back operations. The number of worker's compensation cases, personal injury cases, and private insurance cases should be listed. Preinjury jobs should be subdivided as recommended by Mayer and associates into sedentary to light, light to medium, medium to heavy, and very heavy.[2]

The program dropout rate must be uniformly defined and presented to eliminate biases. Of the number of applicants screened, the program should reveal the number of applicants turned down and the number accepted who dropped out of the program. These numbers represent the program's willingness to accept patients with risk factors for chronicity (injury type, job, demographics, physical findings, and psychological factors)[22] as well as referral patterns. Reasons for dropout should be presented. Outcome measures should include the percentage who returned to work within a week of program completion and the percentage at work or eligible for work six months after program completion.

Program Name _____
6-Month reporting period _____ to _____
_____ Program cost (average for program completers)
_____ Program length (days)
_____ Program intensity (hours/day)
Staff: ___ MD ___ PT ___ OT ___ Psychologist ___ Social Worker
___ Vocational Counselor ___ Exercise Physiologist
___ Nurse ___ Others _____

	Acute 0-6 wk	Subacute 7-12 wk	Chronic 12 wk
Patients			
Number screened	___	___	___
Number declined	___	___	___
Number admitted	___	___	___
Number dropped	___	___	___
Of those admitted			
% Men	___	___	___
Age, yr (standard deviation)	___(___)	___(___)	___(___)
Number postsurgery	___	___	___
Job types			
% Sedentary-light	___	___	___
% Light-medium	___	___	___
% Medium-heavy	___	___	___
% Very heavy	___	___	___
Results			
% Working at discharge*	___	___	___
% Working at 6 months†	___	___	___

*Includes persons at work within 1 week of discharge.
†Includes persons at work or eligible to work but unemployed at 6 months after discharge.

Figure 1.—A model of a report to consumers is shown for those participating in worker rehabilitation programs. This report would be used to inform third-party payers and employers of the progress of a program.

Worker rehabilitation programs are highly motivated to demonstrate their effectiveness to referral sources. Their methods for doing so are often too variable to make meaningful comparisons between programs. The report to consumers included here provides a standardized comparison. It is recommended that referral sources request proof of program quality in this format.

Internal Quality Issues

We have found no study that validates the effect of a quality assurance program. Indeed, only programs that are hospital based, and thus subject to the rules of the Joint Commission on Accreditation of Healthcare Organizations, are under any pressure to do internal quality assurance studies. Until research better defines the factors that relate to quality outcome, regulating forces such as referring physicians, insurers, and accreditation organizations should accept a wide variety of program concepts but insist on an accurate reporting of outcome.

It is intuitive, however, that successful worker rehabilitation programs get that way because of sound concepts, solid clinical skills, and talented administration. We will present without justification issues that are of concern to the managers of some successful programs. Addressing the methods of quality assurance is beyond the scope of this discussion.

Established admission and discharge criteria must be followed. Patients with poor motivation, who are medical risks (cardiac, neurologic, orthopedic, and psychiatric), and those who might benefit more from an alternative therapy should be identified. The program should last for a predefined length and not be prolonged because of issues such as patient pain behavior.

The staff must be experienced enough to separate their role in improving function from the usual role of curing disease. Staff burnout should be anticipated and addressed. The medical director should be effective in educating referrers, screening admissions, supporting anxious patients, dealing with acute events, providing medicolegal documentation, and coordinating the varied talents within the team. If there is no medical director, the administrator must perform some tasks and ensure that referring physicians are capable and willing to assume the others.

Communication with referral sources, insurers, attorneys, and employers must be prompt, accurate, and complete. The effectiveness of patient and family education should be demonstrated. Program components must be effective. The rate of improvement from an exercise program should approximate that of normal persons. Patient effort in areas of strength, endurance, and flexibility should be objectively quantified and addressed constructively.[2] Psychological approaches should result in tested objective improvement.[19]

Ethical and Legal Issues

Worker rehabilitation programs are in a unique and precarious position in the medicolegal system. A number of external factors may significantly affect program outcomes.

Who is the customer? The injured worker is the object of

the treatment, but bills are paid by the employer or the employer's worker's compensation carrier. Rehabilitation specialists who coordinate treatment are hired by the payers. They may operate on structured spending limits that discourage expensive but cost-effective treatments such as functional restoration. The referring physician's and patient's decision to choose a program may be substantially affected by these factors.

What are the goals? Return to work is not necessarily the only obligation in the worker's compensation system. Although compensation laws differ from state to state, medical treatment that improves function in areas outside of work such as household chores and avocational interests may be compensable.

What about the Americans With Disabilities Act?[25] Many workers legitimately fear that when they complete a rehabilitation program their previous employer will not rehire them and, despite their capabilities, other employers will avoid hiring them because of the back injury. Employers are aware that the presence of a previous injury is a risk factor for new injury. Recent federal legislation, the Americans With Disabilities Act, makes it illegal to discriminate against a person with a disability.[26] Although case law will determine the effect of the law, it is likely that an injured worker who is capable of returning to work with reasonable job modifications must be rehired by the employer and must not be discriminated against by future employers. It is hoped that this will not only shift responsibility for disabled persons to the private sector but also reduce the overall cost to society by increasing employment of this group.

When does it all end? Case closure and assignment of a low permanent impairment rating are monetarily beneficial to the insurer but may be financially or emotionally unacceptable to the patient. Functional capacity evaluations, defined as "a measure of function quantitatively by direct or indirect means of a dynamic aspect of bodily activity necessary in daily living,"[2] appear at face value to be useful in case closure. There is no evidence, however, that such tests have predictive value. Programs may be pressured into using data from functional capacity evaluations for case closure.

Conclusion

Referring physicians have a central role in ensuring the quality of a worker rehabilitation program. By properly matching patients with the correct type of program, physicians encourage effective and cost-effective rehabilitation. By demanding sophisticated and meaningful outcome data, physicians ensure that programs are successfully executing the proposed rehabilitation. By understanding some of the internal quality issues, physicians can provide meaningful feedback to the local worker rehabilitation program about areas for improvement. Finally, if they understand the forces, both medical and social, involved in rehabilitating injured workers, referring physicians can act fairly toward all parties.

We advocate a standardized reporting format. The model presented here is designed to be simple for all programs to execute and for referral sources to digest. Some may argue that the format is too simplistic. We would not imply that such a report is bias-proof. A good program that compares poorly with its competitors may wish to provide additional evidence to explain the discrepancy. This evidence should be separated from the basic report format.

It is essential that referring physicians recognize when their abilities to diagnose, treat, and cure do not match patients' needs to be rehabilitated. Early referral reduces suffering, disability, and the multibillion-dollar annual national loss due to occupational low back pain.

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Pain Centers—Organization and Outcome

SRIDHAR V. VASUDEVAN, MD, *and* N. TIMOTHY LYNCH, PhD, *Milwaukee, Wisconsin*

Pain treatment centers have evolved at a rapid rate, but they differ in their complexity and services provided. Patients, as well as primary care physicians, have difficulty in identifying the appropriate center for a specific problem. Guidelines for pain centers have recently been proposed by the International Association for the Study of Pain, along with an attempt at their accreditation. Outcome studies from pain centers have proliferated, with a wide range of treatment programs being reported. Comprehensive multidisciplinary pain centers using the rehabilitation medicine approach are effective in decreasing disability and increasing the productivity of patients with chronic, disabling pain.

(Vasudevan SV, Lynch NT: Pain centers—Organization and outcome, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:532-535)

Primary care physicians frequently see patients whose primary symptom is pain. Evaluating and managing acute pain is an inherent part of every physician's training. Acute pain is a biologically useful warning that provides physicians clues for diagnosis and treatment. With the appropriate control of the underlying pathologic process, pain subsides and resolves, having served a meaningful and useful function.

Frequently patients have pain that lasts beyond the expected duration of healing for a particular injury or illness. In many situations, either no disease can be identified to explain the degree of symptoms or, despite adequate medical and surgical treatment of the identified disorder, pain persists. Patients with chronic and persistent pain tend to challenge the clinical acumen of physicians and frustrate physicians and the health care system. Managing chronic pain, therefore, becomes a challenge not only to the patients but to physicians and society as well.

Acute Versus Chronic Pain

Pain is a complex and puzzling human experience that defies a uniform definition, explanation, or measurement.[1-3] Acute pain can be defined as an unpleasant sensory, perceptual, emotional, and mental experience with associated autonomic, psychological, and behavioral responses provoked by acute disease or injury.[4,5] All pain phenomena include a psychophysiologic experience involving not only nociception, the perception of noxious stimuli, but also the interpretation of those sensations as painful, the evaluation of pain as creating suffering, and antalgic behavior—overt expressions or communication of pain, including posture, grimacing, verbal complaints, avoidance, and the use of assistive devices such as transcutaneous electrical nerve stimulation (TENS), canes, and wheelchairs.[6]

Acute pain serves a biologic function and is useful to both patients and physicians. It subsides and resolves after the underlying pathologic process is adequately treated through medical, surgical, or physical means.

In contrast, chronic pain is persistent and lasts beyond the normal healing period. Chronic pain begins originally as acute pain, often with a typical injury, inflammation, or surgical incision. It differs from acute pain in etiology, mechanisms, pathophysiology, diagnosis, and treatment.[1-6] Chronic pain is not adequately relieved with somatic medical or surgical therapies. Psychological changes in these patients do not seem to respond to traditional psychiatric techniques.[2,6]

More than 70 million persons have chronic pain.[1,2,4] Bonica estimates that 700 million workdays are lost and that the total cost of health care approximates $60 billion annually.[4] A patient with chronic pain is typically in the prime of life, has a history of work-related injury, and has several of the following *D*'s:

- Dramatic pain behaviors;
- Dysfunction demonstrated by badges, collars, braces, or canes;
- Drug misuse;
- Dependency on family and society;
- Deconditioning;
- Disuse of an extremity;
- Depression characterized by sleep disturbances, low energy level, hopelessness, and decreased self-esteem; and
- Disability that far exceeds the underlying biomedical findings.[1-3]

Table 1 summarizes the features seen in persons with chronic pain.[6]

Managing Chronic Pain

The most notable advance in the management of chronic pain is the recognition of psychological and behavioral factors affecting patients.[1,3,5] In the past three decades the management of chronic pain has not only been recognized as different from but uses principles exactly the opposite of those used in acute pain (Table 2). Although the basic tenets of acute pain management include rest, symptomatic relief through medications, avoiding stressful situations, and attention to pain, chronic pain management involves reconditioning, avoiding symptomatic medication therapy for pain, focusing back to a more useful productive role, and avoiding attention to pain behaviors.[1,2,6]

From the Department of Physical Medicine and Rehabilitation, St Joseph's Hospital (Dr Vasudevan), Departments of Physical Medicine and Rehabilitation (Dr Vasudevan) and Anesthesiology (Dr Lynch), Medical College of Wisconsin, Milwaukee, and the Department of Psychology, Pain Rehabilitation Center, Elmbrook Memorial Hospital (Dr Lynch), Brookfield, Wisconsin.

Reprint requests to Sridhar V Vasudevan, MD, Chair, Department of Physical Medicine and Rehabilitation, St Joseph's Hospital, 5000 W Chambers St, Milwaukee, WI 53210.

ABBREVIATIONS USED IN TEXT

IASP = International Association for the Study of Pain
TENS = transcutaneous electrical nerve stimulation

An important step in the treatment of chronic pain is differentiating it from acute pain. This is followed by appropriate counseling of patients and families. Elsewhere we have described guidelines for counseling patients with chronic pain using the "Milwaukee" approach.[7] The following features need to be recognized and accepted by physicians treating patients who have chronic pain:

- The multidimensional nature of pain with sensory, cognitive, behavioral, and environmental factors;
- The biopsychosocial features of chronic pain;
- The differences between acute and chronic pain;
- Life-style changes seen in patients with chronic pain—drug misuse, dysfunction, depression, disability;
- The role of central and peripheral mechanisms in modifying pain;
- Differences in management between acute and chronic pain;
- Role of work, family, and society in patients' pain.

Results of Chronic Pain Treatment Programs

A number of studies have reported results of chronic pain treatment programs. Swanson and co-workers, in a study of 50 inpatients, concluded that half the patients who completed the program were able to return home and increase their work-related activity without taking more drugs or returning to the pattern of frequent visits to physicians and repeated hospital admissions.[8] Seres and Newman, in a study involving operant conditioning, spousal participation, exercise, biofeedback therapy, relaxation therapy, education, the use of TENS, and psychotherapy, reported a reduction in medication, increased activity levels, and a decrease in pain behaviors.[9]

Vasudevan and co-workers, in a study of 78 patients in an outpatient program, concluded that an outpatient program may be cost-effective, but for patients with significant medication dependence, excessive pain behaviors, and residing a long distance from the treatment facility, a structured inpatient rehabilitation program may be required.[10] Järvikoski and colleagues also emphasized that outpatient treatment is suitable for patients with less distress whereas inpatient programs may be needed for those with serious psychosocial distress and those who require a more structured environment.[11]

TABLE 1.—*Common Features of Patients With Chronic Pain**

Have pain of several months' or years' duration
Have pain similar to the initial pain that is associated with a medical problem or injury
History of many treatment failures provided in great detail
Many medications tried, with minimal to poor response
Continuous use of analgesics and tranquilizers, despite patients' testimony that the medications offer no notable or long-lasting relief
Pain described as being unbearable and incapacitating
Strong belief that pain has an unidentified organic cause
Desire and willingness expressed to undergo "any treatment" for pain relief
Claim that everything will be fine if only the "doctor would treat my pain"
Pain not relieved by any medical or surgical treatment
Substantial psychosocial changes present, especially depression, although patients vehemently deny the label; they frequently do admit to feeling frustrated, angry, and irritable, with disturbed sleep, altered moods, weight changes, decreased energy, decreased physical, social and recreational, and sexual activities, and increased family stresses and economic difficulties

*From Gildenberg and DeVaul.[6]

TABLE 2.—*Principles of Management of Chronic Pain*

Cessation of narcotic intake—eliminate potentially addicting narcotics, tranquilizers, and other medications
Encourage an increase in activity levels; graded exercises are provided with education in differentiating "hurt" from "harm"
Avoid use of passive modalities such as heat, massage, or traction; instead, use electrical stimulation such as TENS, biofeedback-assisted relaxation exercises, and sympathetic and epidural blockade
Psychological and cognitive behavioral intervention with group therapy provide insight and operant conditioning principles to shape healthy behaviors
Return patients to meaningful roles, either to work when possible or to more productive life-style

TENS = transcutaneous electrical nerve stimulation

Guck and associates reported the findings of a survey comparing treatment with nontreatment control groups.[12] Considerably more treated patients than untreated patients were employed at follow-up. In addition, treated patients reported less pain-related interference with work, household chores, recreational activities, sexual relationships, physical exercise, and the ability to sleep than did the untreated group. Similarly, the treated group was admitted to hospital significantly less often at follow-up than was the untreated group. Fewer treated than nontreated patients were using prescription narcotics and psychotropic medications after treatment.[12]

Stieg recently discussed the problems in defining cost-effectiveness in this age of ever-increasing accountability.[13] Of all the pain centers in the United States recently listed in a published directory, less than 5% were accredited by either the Joint Commission on Accreditation of Health Care Organizations or the Commission on Accreditation of Rehabilitation Facilities. Stieg also identifies the problems in comparing pain centers in that many dedicated pain treatment centers have no professional staff who belong to any of the scientific organizations that serve the pain population.[13]

Outcome studies are confounded by the fact that patients with chronic pain seem to be treated as a homogeneous group with generic treatments. Turk attempts to classify the subgroups of patients with chronic pain along with suggesting possibly customizing the therapeutic intervention to a patient's characteristics.[14] Thus, future outcome studies need to address these subgroups of chronic pain and require prospective cost-effective research matching the treatment with patients' characteristics.

Pain Centers

Since the original concept of multidisciplinary pain centers evolved in the early 1960s, there has been a notable proliferation of facilities that evaluate and manage pain. This development has occurred worldwide but predominantly in the United States. The International Association for the Study of Pain (IASP) recently published the results of a task force on guidelines for the desirable characteristics for pain treatment facilities.[15]

Pain centers vary in their complexity of setting, staffing,

and costs. Some are unimodality clinics, and others are comprehensive treatment and research facilities. One way to classify pain centers is by their approach to treatment—whether they use a pathophysiologic, psychiatric-psychological, or rehabilitation model.

Pathophysiologic treatment facilities use treatment approaches directed at a peripheral nociceptive disorder. Many "nerve block clinics" would fall into this category. Such programs address acute pain and postoperative pain and some selective phases of chronic pain. The approach is intended to reverse a pathophysiologic process, however, and does not address the complexity of the chronic pain phenomenon discussed earlier.

The psychiatrically or psychologically oriented approach views pain as an expression of underlying psychological conflict and distress. Patients are given appropriate psychotropic medication and long-term counseling. Patients with chronic pain would not be candidates for a treatment facility using such an approach.

The rehabilitation model of pain treatment facility addresses not only the medical but the physical, psychological, social, vocational, and economic aspects of patients with pain-related disability and their families. The goal is to improve patients' function, decrease dependency on health care personnel, increase physical activities, and return patients to their "usual" roles.

There is no uniform method of accreditation or certification of pain facilities. Pain facilities may obtain voluntary certification from the Commission on Accreditation of Rehabilitation Facilities,[16] but this commission provides standards only for the rehabilitation model of chronic pain facilities. Because of the lack of accreditation, pain management has been viewed with skepticism by physicians and health policy and funding administrators, thus prompting the IASP to provide reasonable guidelines for pain treatment facilities.[15]

The IASP guidelines identify the following desirable characteristics of pain centers[15]:

- A multidisciplinary pain center is an organization of health care professionals and basic scientists that includes research, teaching, and patient care related to acute and chronic pain. The clinical programs need to be supervised by an appropriately trained and licensed clinical director with a wide array of health care specialists such as physicians, psychologists, nurses, physical therapists, occupational therapists, vocational counselors, social workers, and other specialized health care providers. These centers are affiliated with major health sciences institutions and provide evaluation and inpatient and outpatient programs.
- A multidisciplinary pain clinic is a "health care delivery facility staffed by physicians of different specialties and other nonphysician health care providers who specialize in the diagnosis and management of patients with chronic pain."[15] This differs from the multidisciplinary pain center in that it does not include research and teaching activities in its regular programs. The services may be provided on an outpatient or inpatient basis, or both.
- A pain clinic is a "health care delivery facility focusing upon diagnosis and management of patients with chronic pain."[15] A pain clinic may specialize in specific diagnoses or pain related to a specific region of the body. The IASP guidelines strongly emphasize that this label should not be used for a solo practitioner. In such a program, interdisciplinary assessment and management are absent.
- A modality-oriented clinic is a "health care facility which offers a specific type of treatment and does not provide comprehensive assessment or management."[15] Examples suggested are nerve block clinics, TENS clinics, acupuncture clinics, or biofeedback clinics.[15] Again, the major emphasis is the lack of an integrated, comprehensive interdisciplinary approach.

TABLE 3.—*Choosing a Pain Treatment Facility*

Does the pain treatment facility provide a comprehensive range of programs: evaluation only, inpatient, full-day outpatient, individualized program?
Is there an identified medical director who has obtained recognized board certification and training in pain management?
Does the medical director belong to a nationally recognized pain organization and attend meetings of these organizations?
Does the facility have a variety of other health care professionals? At the minimum, are there psychologists, nurses, physical therapists, and occupational therapists, and are different medical specialists available for consultation?
Does the facility have a mechanism for interdisciplinary communication through team conferences?
Is there sufficient space for the activities of the program either on premises or through an affiliation?
Does the facility deal with a wide variety of chronic pain patients or is it limited to only specific diagnoses?
Is the center involved in research activities, and does it make the results of its program available?
Does the facility participate in educational programs for the community at a variety of levels?
Is the facility affiliated with a major health research facility, tertiary facility, or university?
Does it offer a variety of treatment approaches, such as detoxification, pharmacotherapy, physical conditioning, and psychological counseling?
Does the facility have a follow-up program?
Is there a support group for graduates of the program?
Is the facility accredited by nationally recognized organizations?

The IASP task force strongly emphasizes the need for a multidisciplinary approach to the diagnosis and treatment of patients with chronic pain. Although not every patient referred to such a facility would need all the services, these guidelines encourage the facilities to have the resources available when they become appropriate. In addition, health care professionals in pain treatment facilities are encouraged and expected to become members of IASP and its national chapters to facilitate the exchange of information and research activities.

Examples of questions physicians (and patients) may wish to consider in choosing a pain treatment facility are given in Table 3.

Conclusions

The rehabilitation of patients with chronic pain requires that primary care physicians understand and recognize the pluridimensional nature of pain. Outcome studies from chronic pain programs have shown substantial improvement in the functional status of patients and decreased disability. Pain treatment facilities vary in their comprehensiveness, and primary care physicians need to recognize the mechanisms for identifying an appropriate treatment facility for their patients with chronic pain. Physicians should be able to recognize chronic pain, communicate and counsel patients and their families appropriately in establishing realistic

goals, and use the resources of the pain treatment facilities in the community to decrease disability and improve the quality of life of these patients.

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A QUADRIPLEGIC'S NIGHTMARE

I speed past the others,
an eagle in flight.
I break through the ribbon,
and conquer the night.

My legs become heavy,
arms fall to my side.
I question my future,
cannot stay on this ride.

I open my eyes,
and my body is gone,
lost by my carelessness,
now it is dawn.

I have little left,
what's here's hard to find,
will I discharge the rest
and give up my mind?

JAMES TROESH©
Hacienda Heights, California

Use It or Lose It—The Hazards of Bed Rest and Inactivity

PAUL J. CORCORAN, MD, *Boston, Massachusetts*

Professional experience and lay wisdom teach us the benefits of exercise and the hazards of idleness. Yet the myth persists that "bed rest is good for you" when ill or convalescing. Abundant scientific evidence in the past 50 years has demonstrated the specific damage done to each of the body's organ systems by inactivity. Both aging and inactivity lead to strikingly similar kinds of deterioration. I summarize the data from military and veterans' hospitals, rehabilitation experience, aerospace research, and gerontology and review the physiologic and metabolic changes of aging and inactivity, along with strategies to help prevent the iatrogenic complications of bed rest.

(Corcoran PJ: Use it or lose it—The hazards of bed rest and inactivity, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:536-538)

Look at a patient lying in bed.
What a pathetic picture he makes.
The blood clotting in his veins,
the lime draining from his bones,
the scybala stacking up in his colon,
the flesh rotting from his sweat,
the urine leaking from his distended bladder,
and the spirit evaporating from his soul.

RICHARD ASHER, MD[1]

Most people take for granted the assumption that rest is beneficial in restoring the health of an ill or injured person. The bed is the central focus of hospitals and the standard unit of size for health care facilities. On admission, patients are shown to their beds, their clothing is taken away, and skimpy gowns are provided. Hospital procedures and expectations sharply curtail mobility. Even ambulatory patients generally remain under the sheets, if only for warmth and modesty.

Before the 1940s, strict bed rest was the rule for two weeks after childbirth, three weeks after herniorrhaphy, and four weeks or more after myocardial infarction. The shortages of hospital beds and personnel during World War II led to the surprise discovery that early mobilization of the sick and injured actually improved results and lessened complications. Postwar rehabilitation programs in the Veterans Administration hospitals taught that the avoidable complications of bed rest were often more disabling than the original injury. Deitrick and colleagues, in a classic study of immobilized healthy young men and seriously ill polio patients, documented striking metabolic and neuromuscular deterioration.[2] More recent research by the National Aeronautics and Space Administration (NASA) produced additional evidence for the damaging effects of prolonged inactivity and weightlessness.[3] In the 1980s, the extremely early hospital discharges caused by the diagnosis-related group system of prospective payment have pushed early ambulation to the limit, causing considerable inconvenience and discomfort but little documented evidence of harm.

Short-term benefits may result from limited rest of individual body parts: elevating the legs to treat shock, eliminating gravity in peripheral edema, relieving abdominal wall pressure after laparotomy, or resting traumatized soft tissues or skeletal structures. The severity of an illness may leave no choice except bed rest, but the rest itself is rarely beneficial. On the contrary, virtually every organ and body system promptly and progressively deteriorates when inactivated (Table 1).[4]

Effect of Rest on Body Systems

Joints and Connective Tissues

The moving parts of the body—joints, ligaments, tendons, muscle, and skin—all have a normal range of motion that is necessary for the proper performance of physical tasks. Any decrease in the normal range of motion is designated a *contracture*. Contractures may be anticipated side effects of necessary treatment, such as a knee contracture after plaster immobilization. More often, contractures are produced unwittingly and unnecessarily—the frozen shoulder caused by the use of a sling to treat a Colles' fracture of the wrist, for example.

Contractures probably begin forming within eight hours, as illustrated by the morning stiffness after a night's sleep, but this can be reversed by a single range-of-motion exercise,

TABLE 1.—*Unnecessary Additional Disabilities Due to Bed Rest*

Joints	Contractures: loss of normal range of motion
Muscles	Disease atrophy: 15% loss per week of inactivity
Bone	Osteoporosis; pathologic fractures
Urinary tract	Infection; calculosis
Heart	Deconditioning: decreased cardiac reserve; decreased stroke volume; resting and postexercise tachycardia
Circulation	Orthostatic hypotension; thrombophlebitis
Lung	Pulmonary embolism; atelectasis; pneumonia
Gastrointestinal	Anorexia; hospital-acquired malnutrition; constipation, impaction
Skin	Decubitus ulcer
Psyche	Anxiety, depression; disorientation

From the Departments of Rehabilitation Medicine, Tufts University School of Medicine, Boston, and the New England Sinai Hospital and Rehabilitation Center, Stoughton, Massachusetts

Reprint requests to Paul J. Corcoran, MD, Department of Rehabilitation Medicine, New England Sinai Hospital and Rehabilitation Center, 150 York St, Stoughton, MA 02072.

the pleasurable morning stretch when we first get out of bed. The rate of contracture formation is accelerated by several factors that often may coexist in the immobilized parts: edema, bleeding, infection, burns, or the healing of traumatic or surgical wounds.

Contractures are corrected by therapeutic heating—to increase the compliance or "stretchability" of collagen fibers—followed by range-of-motion exercises. Serial casting or adjustable orthotic devices may be necessary in more severe cases, and surgical correction is occasionally required.

Range-of-motion exercises can be encouraged or done by nursing staff as part of routine care. Proper positioning does not prevent contractures but may cause them to occur at a less undesirable angle. The best prevention is early ambulation, bathroom privileges, and self-care activities that require patients to use and maintain their full range of motion.

Muscles

A muscle is only as strong as it needs to be for the tasks it regularly does. Disuse atrophy leads to the loss of about an eighth of a muscle's strength with each week of total inactivity. A partially used muscle exerting less than 20% of its maximum force will begin to atrophy, whereas regular exertion at 20% to 30% of maximum force will preserve a muscle's strength.

Backache after bed confinement is commonly caused by disuse weakness of paraspinal and abdominal muscles; this, of course, limits the usefulness of bed rest in the treatment of low back pain. Physical therapy may prevent disuse atrophy, but simple out-of-bed orders, bathroom privileges, or bedside commode prescriptions can do much to retard its progression.

Bones

Bone is a dynamic tissue that undergoes continual deposition and replacement, in response to the dual stimuli of weight bearing and muscle pull. After bed confinement, calcium loss from bone begins immediately, and increased urinary clearance of calcium is detectable within a few days. This can lead to urolithiasis and heterotopic calcification. Calcium clearance is four to six times normal within three weeks of total immobilization.[2] More gradual calcium loss accompanies the declining activity of age or chronic illness and accounts for the frequency of hip and vertebral fractures in the elderly.

Urinary Tract

The ureters empty by peristalsis, but the renal pelvis drains entirely by gravity. In a recumbent patient, loss of this gravitational emptying leads to stagnation in the calyces. This predisposes patients to calculus formation and infection. Bladder emptying may also be incomplete when voiding has to be done in a supine position on a bedpan or into a urine bottle. These risks can be lessened by frequent turning, sitting up in a chair, or the use of a bathroom or a bedside commode in preference to the bedpan. Adequate fluid intake and intermittent catheterization of the neurogenic bladder are additional preventive measures.

Heart and Circulatory System

Like other muscles, the heart undergoes disuse atrophy when patients become inactive. Studies done by NASA before the first manned space flight showed that after three weeks of bed rest, stroke volume fell, causing the heart rate to rise by 10 beats per minute.[3] Postexertion heart rates were 40 beats per minute greater than before the bed rest. Exercise tolerance did not return to normal again until after five to ten weeks of vigorous reconditioning.

Peripheral and pelvic venous thrombosis probably occurs to some extent in every bed-bound patient, and pulmonary embolism is the commonest cause of sudden, unexpected death of patients in hospital.[5] Orthostatic hypotension is another result of recumbency or weightlessness. The use of anticoagulants and elastic stockings can prevent or treat these complications, but the best prevention is to limit the duration of bed rest and inactivity.

Lungs

The mucous film lining the smaller air passages tends to pool when patients lie in one position, leading to local atelectasis. Sedation and dehydration accelerate this process. The work of respiration is greater in recumbency than when a person is sitting, and deep breaths and sighs occur less frequently. Atelectasis and pneumonia are well-known complications of bed rest, even in the absence of preexisting pulmonary disease. Pulmonary embolism and aspiration pneumonitis are other complications of bed rest. Preventive measures include frequent turning, maintenance of adequate fluid intake, respiratory therapy for high-risk patients, and early mobilization of bed-bound patients.

Gastrointestinal Tract

Documented effects of bed rest include diminished appetite and fluid intake. Swallowing may be difficult in the reclining position. Peristalsis decreases with inactivity. Constipation and malnutrition are familiar features of debilitated bed-bound patients.

Skin

Capillary filling pressures range from about 18 to 35 mm of mercury, or about 0.5 lb per in^2. Thus, a 150-lb body would need 300 in^2 of skin surface to avoid compressing skin capillaries. Skin circulation is obstructed, and skin perfusion ceases over the bony prominences of a recumbent patient, causing infarction of the skin—bedsores. Air-fluidized beds can prevent this, and alternating pressure air mattresses may help, but turning the patient at least every two hours is the simplest and safest approach. Egg-crate foam mattresses and protective foot cradles provide additional protection, but getting the patient out of bed is the best preventive.

Psyche

At NASA, studies of normal young men who were kept in bed for five weeks showed significant increases in anxiety, hostility, and depression, together with altered sleep patterns.[6] Bed rest appears to be a subtle form of sensory deprivation. Of interest is that exercising during bed rest reduced these deleterious effects considerably.[7]

A longer-term psychological consequence of bed rest is the "learned helplessness" sometimes seen in patients after prolonged hospital stays. Bed-bound patients are expected to play a sick role. The "good" patient is docile and compliant, taking medications and following professional orders without questions. Care providers are likely to reinforce this sick behavior and react negatively to patients who attempt to manipulate or challenge hospital routines. Bed-bound patients

lose control over the most intimate aspects of their lives: external forces control their diets, sleep, money, social contacts, and sexual expression. Medications, appointments, and health records are managed by others. Small wonder that many patients have trouble resuming independent management and decision making after prolonged bed rest.

Other Diseases Associated With Inactivity

Reflex sympathetic dystrophy or "causalgia" after a neurologic injury is much more common if the injured limb, or the entire patient, has been immobilized. The fibrositis-fibromyalgia syndromes are associated with inactivity. The hypochondriac behavior pattern known as "compensitis" leads to many of the physical complications listed above, when financial secondary gain encourages inactivity. Most chronic pain syndromes begin during periods of bed rest or diminished activity and respond therapeutically to increased activity. Depression and inactivity are intimately connected, and physical activity has proven therapeutic value in the treatment of depression.

Aging and Disuse

Bortz and others have called attention to the remarkable similarity between the physiologic effects of aging and the changes found after inactivity.[8] A lifetime of exercise, or a therapeutic exercise program after a period of inactivity, will retard or reverse these changes, even in an aged person.

In the cardiovascular system, both disuse and aging lower the maximum oxygen uptake, cardiac output, and stroke volume and raise the blood pressure due to increased peripheral resistance. Erythropoiesis and red cell mass diminish, protective fibrinolytic activity is reduced, and serum cholesterol and triglyceride levels increase. Both aging and disuse change the body composition and metabolism in similar ways: decreased lean body mass, increased body fat, calcium loss, decreased cortical thickness of bone, decreased glucose tolerance, lowered mean body temperature, and diminished serum androgen levels with decreased spermatogenesis and libido.

There is a substantial decrease in the central nervous system content of the neurotransmitters dopamine, norepinephrine, and serotonin both in aging and after inactivity. Both conditions decrease the dominant frequency of the electroencephalogram and lead to disordered sleep patterns. Auditory thresholds increase, taste sensitivity drops, and intellectual capacity is lowered, with diminished memory and increased depression. The actin and myosin content of the myofibrils decreases both with aging and with disuse, and there is a decrease in the cross-sectional area of muscle fibers, connective tissues, and overall muscle size. The muscle capillary beds shrink considerably both in aging and disuse, leading to the increased peripheral resistance and the elevated blood pressures associated with both states. Frontera and co-workers have shown that these changes can be reversed through exercise, even in the aged.[9]

TABLE 2.—*Strategies for Minimizing Harmful Effects of Bed Rest*

Minimize duration of bed rest
Avoid strict bed rest unless absolutely necessary
Allow bathroom privileges or bedside commode
Stand the patient for 30 to 60 seconds whenever transferring from bed to chair
Encourage the wearing of street clothes
Encourage taking meals at a table (not in bed)
Encourage walking to hospital appointments
Encourage passes out of the hospital on evenings and weekends
Order physical therapy and occupational therapy as needed
Encourage daily range-of-motion exercises as a basic part of good nursing care

Conclusion

In the past 50 years, there has been a complete reversal of the role of bed rest in the health care system. Initial stimuli for these changes have been largely nonmedical—war, manned space flight, or health care cost containment. Serendipity and research have shown that inactivity is harmful and that early ambulation and exercise can prevent many of the complications of both disuse and aging. Regrettably, everyday practices and attitudes have not caught up with scientific knowledge, and bed rest and immobilization are still overused by patients and physicians. The fitness craze is principally a phenomenon of young adults, and most of us still accept the spreading waistlines and sagging capacities of midlife as inevitable results of aging.

Bortz concluded his survey on disuse and aging with the observation that, while physical inactivity is not the cause of the aging process and it is wrong to suggest that exercise might "halt the fall of the grains of sand in the hourglass," nevertheless, the toning influence of physical activity may cause the sand to drain more slowly; and a physically active life may allow us to approach our true biogenetic potential for longevity.[7]

Much can be done in our daily patient care to prevent the complications of inactivity and bed rest (Table 2). Asher composed an appropriate physician's prayer:

Teach us to live that we may dread
unnecessary time in bed.
Get people up and we may save
our patients from an early grave.[1]

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Pressure Sores—A Multifaceted Approach to Prevention and Treatment

WILLIAM E. STAAS, Jr, MD, *and* HELEN M. CIOSCHI, MSN, CRNP, *Philadelphia, Pennsylvania*

The incidence and effect of pressure sores on the disabled and elderly population have created a challenge to physicians and health care professionals, from emergency departments to rehabilitation units, and in the community. If not prevented, the morbidity and mortality of patients and the direct and indirect costs to both patients and the health care system are radically increased.

In this article we define the impact on our health care system of pressure sores, provide an overview of a multifaceted approach to their prevention and management, and introduce successful behavioral and educational approaches for patients with chronic, recurrent sores. A coordinated approach with patients as informed participants and their care givers enhances the chances for success.

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Pressure sores continue to be a major societal health problem, greatly affecting patients and their caretakers. Pressure sores are a major cause of admissions to hospitals for patients with impaired mobility and sensory function and for elderly patients. In 1987, more than 532,000 Medicare hospital days were used by patients having pressure sores or decubitus ulcers as the primary diagnosis. In addition, about 1,759,000 Medicare hospital days were used with pressure sore or decubitus ulcer as the secondary diagnosis. Direct charges associated with each of these categories range from $3.4 million to $1.1 billion dollars.[1] Beyond the cost issues, pressure sores are associated with a high mortality rate. Allman and co-workers identified mortality rates ranging from 23% to 37% related to elderly patients being admitted to hospitals and to institutions with pressure sores.[2] According to Brody, if "untreated or allowed to reach advanced stages, bedsores can result in life-threatening complications that cause an estimated 60,000 deaths a year" (J.E. Brody, "Personal Health," *New York Times*, August 6, 1986, p C-6).

As a result of increased knowledge regarding the causative factors and critical determinants of pressure sores, there has been an altered focus in the management of pressure sores from one of treatment only to prevention and early intervention. Pressure sores are not simply a natural sequela of disease and disability. Critical risk factors, both intrinsic and extrinsic, are now known by most physicians, nurses, and other health care professionals. Accordingly, it is incumbent on health care professionals to identify, protect, and educate those persons at risk. As the public becomes more knowledgeable about optimal health care outcomes, disease prevention, and containing health care costs, it will also demand a proactive rather than reactive approach to maintaining skin integrity and preventing this costly complication. In Brody's article, in which she discusses the concerns related to the prevention rather than the cure of pressure sores, she instructs the public to "insist that appropriate preventive steps be taken and [to] check periodically to see that they are consistently practiced." This message serves patients well in that their knowledge of potential complications may result in changes in reactions to hospital stays and disability as they seek and demand preventive interventions rather than expensive curative approaches.

The adage "an ounce of prevention is worth a pound of cure" relates well to this important problem in terms of cost and morbidity and mortality. The costs associated with pressure sores, however, are not strictly financial. Pressure sores also have a considerable impact on lost personal time for patients and care givers. Many nursing care hours are taken up with the prevention and treatment of this problem. Nurse specialty groups, including the Association of Rehabilitation Nurses and the Association of Enterostomal Therapists, have recognized and responded to the need for specialty education and collaborative research with the pharmaceutical and medical equipment industries regarding specialty beds, cushions, and the like to prevent this complication and to manage it appropriately and in a timely manner. The Medicare prospective payment system has also fostered a restrictive approach toward this problem, as patients with pressure sores are frequently confronted with limited reimbursement and limited hospital days. Prevention techniques must be used to reduce hospital costs and to effect optimal patient outcomes. Pressures imposed by the prospective payment system have resulted in the premature discharge of patients to the community. Caretakers have demonstrated the ability to manage pressure sores in the home setting. If pressure sore management becomes complex, however, families or care givers may consider sending the patients to institutions. This poses a difficult problem for caretakers because many extended care facilities will not admit patients who have extensive pressure sores.

Pressure sores are often a secondary complication for persons with disabilities. Perhaps the disability most investi-

From the Magee Rehabilitation Hospital, Philadelphia, Pennsylvania.
Reprint requests to William E. Staas, Jr, MD, President and Medical Director, Magee Rehabilitation Hospital, 6 Franklin Plaza, Philadelphia, PA 19102.

gated has been spinal cord injury. Despite more than 40 years of research in the area of tissue or pressure sore research related to spinal cord injuries, preventable pressure sores continue to be a major cause of hospital admissions, temporary alterations in life-style, and lost vocational time in this population. About 30% of all persons with spinal cord injuries will have pressure sores develop during the years immediately after their initial rehabilitation program. Young and Burns reported that at least 5% to 7% of those persons will require readmission to a hospital for the management of severe pressure sores during their follow-up years.[3,4] Reuler and Cooney found that the complications of pressure sores are multiple and life-threatening and account for 7% to 8% of the deaths of persons with spinal cord injuries.[5]

Costs associated with pressure sore management in patients disabled with spinal cord injuries are also staggering. These costs are typically based on the duration of hospital stay and direct costs of these hospital stays. Reports identifying costs do not provide complete data as they relate to actual total costs, such as consultant, special medical or surgical, and anesthesia costs. In any event, escalating costs are apparent as evidenced by reported estimates per admission of $15,000 in 1969, $30,000 in 1982, and, most recently, $120,000 in 1988.[6]

Although these costs are staggering, the costs to patients in lost income, productivity, progress towards vocational goals, independence, and self-esteem are also significant.[7] According to Redd and Woodbury, persons who sustain spinal cord injuries are typically young adults who, notwithstanding their injury, must come to terms with the process of physical maturation and expression and self-esteem through physical activities. Pressure sores interfere with these developmental activities.[8] The patients are constantly faced with the need to prevent skin breakdown. They should be instructed in their initial rehabilitation program to learn and apply preventive skills, to develop a new repertoire of behavioral approaches for keeping healthy, and to know when and how to intervene if signs of impending skin breakdown are identified.

As stated earlier, there is increased awareness of prevention and treatment interventions by health care professionals. Despite this, many persons with traumatic or progressive disability may not have been instructed in assessing normal states, recognizing changes from the norm, exploring the cause, seeking help, and taking action to prevent further trauma or illness. There are also instances wherein the ability to adhere to a basic regimen is not present because of a lack of support systems or personal dedication to follow through with these activities.

Classifications of Pressure Sores

Various classification systems exist to define the degree (grade) of a pressure sore. Each classification system is limited in that while they describe the extent of tissue damage as it relates to tissue and bone involvement, they do not provide descriptive wound characteristics. Classification systems are also restrictive in that they do not describe the causative factors related to the sore development. A commonly used grading system devised by Shea[9] is as follows:

- Grade I .... Limited to superficial epidermis and dermal layers
- Grade II.... Involving the epidermal and dermal layers and extending into the adipose tissue
- Grade III ... Extending through the superficial structures and adipose tissue and down to and including muscle
- Grade IV ... Includes the destruction of all soft tissue structures down to the bone, with communication with bone or surrounding structures.

Shea also describes the closed pressure sore that at the surface appears limited in extent, has some drainage, but covers a large bursalike cavity extending to deep fascia or bone.[9] Other classification systems differentiate grades based on partial or full-thickness tissue involvement, the presence of tracking, and fistula sites.[10]

Despite their limitations, classification systems are essential in defining a wound in a consistent manner. Classifying wounds through the use of one system, at least within a single institution, may assist with assessment and treatment.

Clinical Methods of Measuring Wounds

Various approaches have been used to identify the extent of wound involvement. A simple measurement with a tape measure or acetate ruler, photographs taken serially, and wound tracings provide a limited dimensional perspective. Another method recently described involves volumetric measurement with the use of a saline solution, transparent dressing, and a syringe. This approach, developed by Berg and others, provides practitioners with surface diameters and depth assessment.[11] It is more time-consuming, however, and the assistance of another practitioner is occasionally required to complete the measurement.

Preventive, Medical, and Equipment Interventions for Pressure Sore Management

Interventions directed at pressure sores can be divided into categories that include preventive, medical (both local and systemic), functional (which includes the use of special equipment), and behavioral or educational. Preventive interventions include proper positioning and posturing, frequent weight shifts and pressure relief interventions, prone positioning at night, the elimination of shear and friction activities, the proper use of equipment, and frequent skin inspections. These techniques direct care providers and patients toward the goal of maintaining intact skin. Preventive interventions are directed at educating patients to prevent or reduce the development of pressure sores by avoiding or minimizing the major contributing risk factors of pressure and shear.

Another preventive intervention developed by health care professionals is the use of a risk assessment tool to create awareness and to assess and then direct the health care management. Risk assessment typically involves using scales with rating categories such as mobility, cognition, continence, nutritional status, and activity.[12,13] Each category is given a rating, and the degree of risk for the development of pressure sores is determined by the total score. Scaling is usually done at the time of admission and periodically thereafter. The use of rating scales has been successful in acute and geriatric care settings in predicting persons at risk and possibly preventing the development or further progression of a sore. Patients admitted to rehabilitation centers typically have impaired mobility and sensation and perhaps cognitive impairment; therefore, the sensitivity of these scales in these

settings may require further investigation. More studies of their applicability and validity are needed. As a screening tool, however, the scaling instrument promotes the use of early intervention and reminds evaluators that certain areas must be assessed and monitored on an ongoing basis.

Other preventive interventions include the use of specialty mattresses, overlays and "high tech" beds, and wheelchair cushions. The critical issue of pressure distribution and its effect on pressure sore development has been identified by Kosiak, Lindan, and others.[14,15] The other critical component of "time at pressure" is the intensity and direction of pressure in contributing to pressure sore formation. In Kosiak's study, no changes were noted in tissues subjected to pressures of 35 mm of mercury for as long as four hours or to varying pressures of as much as 190 mm of mercury for an hour.[14] The constant application of a pressure of 70 mm of mercury, however, produced irreversible cellular changes after two hours. This points to the need to frequently relieve pressure over time or to reduce tissue surface pressure. Based on these early studies, most "surface" interventions were directed toward keeping surface pressures below capillary pressures (15 mm of mercury venous to 32 mm arteriolar to reduce the external compression of capillary blood flow and thus to prevent ischemia and necrosis.[16]

During the past 30 years, a variety of mattress overlays, including foam, sheepskin, gel, and air products, has become available. For the most part, these devices provide comfort by partly but not substantially reducing pressure in a supine or side-lying position. They also may decrease pain. Certain studies involving normal, healthy subjects have shown that mean trochanteric and sacral interface pressures at slightly below capillary pressure were achieved in a supine and side-lying static position. One study by Maklebust and colleagues compared the sacral, trochanteric, and heel pressures among hospital mattresses, 2-in foam, a flotation foam pad, and an air cell cushion.[17] In this study, the air cell cushion achieved below capillary pressures for sacral and trochanteric readings. As would be expected, the highest pressures for all mattress overlays were in the heels.

In selecting a product, caution should be exercised about generalizing these results to a compromised patient or to a patient at high risk. A generational growth of these products has led to the development of the high-technology bed, which is typically a hospital bed that is modified to provide pressure relief through a fluidized air system or a pulsating, alternating, and possibly oscillating system. These beds suspend the patient on the support surface, providing the same concept and success as a water mattress. Air fluidized therapy provides for the prevention and management of pressure sores in postsurgical patients with sacral, trochanteric, or ischial rotation flaps; assists with positioning of patients who have severe contractures and spasticity; and provides a comfortable support surface for cancer and burn patients who typically experience pain with repositioning and from constant surface pressure.

The limitations of high technology beds include temperature control, potential dehydration, limited mobility from bed to chair or other surfaces, patient adjustment to flotation, bed design, cost, and limited applicability to the home setting.

The water mattress, or water-filled insert mattress, has been shown to provide significant pressure measurements below capillary closing pressures.[18] In a flotation device, the patient's weight is distributed over a greater surface area, thus decreasing the pressures over bony prominences. According to Staas and LaMantia,

> [S]ome water mattresses when properly inflated will float the patient over the surface with documented mean capillary pressure of 11 mm Hg per square centimeter of body surface in the supine position. Since all water mattresses will not accomplish these low pressures and some mattresses will not have enough structural capacity to float the patient properly, care should be taken in prescribing the proper mattress.[19(p414)]

Although more cost effective, water mattresses, similar to air-fluidized therapy, cause added mobility difficulties such as with transfers, may worsen spasticity, and may cause motion sickness. Despite these limitations, water mattresses may be used effectively in hospitals and in the home. In addition, patients can remain in a supine position for a prolonged period (as long as eight hours) without showing any signs of compromise to the skin.

Regardless of the type of mattress, mattress overlay, pressure-relieving device, or specialty bed, great consideration must be given to the initiation, progression, and assessment of a patient's turning regimen and bed positioning. Patients and care givers should not develop a false sense of comfort through the use of any device, as no device is fail-safe. Before a device is selected, the risk-benefit ratio should be determined by including information regarding pressure measurements, comfort, costs, mobility, and care delivery.

For patients who require wheelchair mobility, static wheelchair cushions are designed to provide some degree of pressure relief and a base of support for posture and mobility. Few cushions achieve these objectives. Wheelchair cushions are either dynamic (alternating pressures dependent on an external source) or static. As defined by Donovan and associates, the primary function of wheelchair cushions is to relieve pressure, distribute weight away from bony prominences, and stabilize the body for balance and functional positioning.[20] As with pressure relief devices for beds, cushions typically fall into the categories of air-filled, flotation-filled, flotation gel, or polyurethane foam.

The role of the wheelchair cushion is to provide a support surface that distributes weight under the ischial tuberosities, buttocks, greater trochanter, and thighs. Pressure readings of 40 to 60 mm of mercury in the ischial area, 60 to 80 mm of mercury in the posterior trochanter, and 80 to 100 mm of mercury over the thighs have been recorded in published studies.[21-23]

Unlike mattress overlays and specialty beds, wheelchair cushions rarely achieve ischial pressure readings below capillary pressure. This is a direct result of the smaller surface area bearing the upper body weight; 50% of the body weight is supported on 8% of the sitting area at or near the ischial tuberosities. Despite cushion use, weight shifting and pressure relief continue to be necessary to avoid pressure sore development. In addition to this, symmetric postural alignment is critical in avoiding uneven weight bearing that leads to ischial, trochanteric, sacral, or trunk pressure sores.

Independent pressure relief for quadriplegic or substantially neurologically impaired patients can be achieved through the use of an electric reclining wheelchair. Technologic advancements have created wheelchair seating systems that significantly reduce or eliminate shearing with back reclining.

The advantages and disadvantages of wheelchair cushions should be evaluated according to their purpose, material,

weight, portability, patients' functional status, cushion durability, and initial and replacement costs. Patients need to be educated on their proper use and on when to seek help with wheelchair cushion management (including repairs). Changes in physical status, changes in posture due to age, contractures, spasticity, or surgical skin repair, and changes in activities of daily living may necessitate reevaluating a cushion in use. Specialty clinics have been developed that manage equipment issues related to wheelchairs and cushions and provide patients with the opportunity for an annual equipment evaluation if needed.

The literature also describes the availability of certain devices directed at training patients to do wheelchair push-up exercises to relieve pressure at recommended intervals of 30 minutes. These newer systems record the frequency of weight shifts and remind patients with alarm sounds to perform pressure relief interventions.[24] Although these devices may be used in rehabilitation programs to train patients to incorporate these behaviors into activities of daily living, they have only limited use in the community.

Medical Management of Pressure Sores

Managing preexisting medical conditions is essential for the optimal healing of wounds and for the prevention of pressure sores. Certain medical problems that contribute to the development of pressure sores include, but are not limited to, altered cognition; altered sensation and mobility; hemodynamic changes; anemia; edema; musculoskeletal problems including contractures, heterotopic ossification, and spasticity; infection; malnutrition—undernourished or overnourished—incontinence; and iatrogenic causes. Aging patients, trauma patients, and neurologically impaired patients typically experience many of these problems throughout their hospital stays and in the community. The early recognition of these medical problems will help to reduce the risks of pressure sores.

The field of the medical management of pressure sores and wounds is rapidly growing and changing. Controversy continues over the use of cleansing agents, wet to dry dressings, and certain topical agents for the management of wounds. Although various articles identify the potential cytotoxicity of these agents, many practitioners continue to use solutions to cleanse the wound and to provide bacteriostatic control. According to Baxter and Rodeheaver,

> Antiseptic solutions and washing agents, such as free iodine, alcohol, merbromin, chlorhexidine, soaps/detergents, and hydrogen peroxide, while suitable for healthy, unbroken skin surrounding the wound, are too caustic for the wound itself.[25(p73)]

In addition, the authors say the actual volume and force of irrigation are more important than the solution itself for cleansing the wound of debris, necrotic tissue, and bacteria. They also question the use of topical antibiotics in wound management and recommend that, due to their unestablished efficacy, they should be used cautiously and for a limited time. When a clinical infection is suspected, the use of parenteral antibiotics should be considered.

Wound cleansing and debridement are usually provided through mechanical, chemical, or autolytic means. Mechanical debridement typically includes surgical debridement, irrigation with a saline solution and other agents, and wet to dry dressings. These methods are effective in removing necrotic tissue so that a wound bed for stimulating granulation is provided. Chemical debridement includes the use of enzyme preparations that break down fibrin clots and exudate, providing an optimal wound environment for new tissue growth. These agents must be used cautiously, however, because they may be nonselective and could impair new tissue growth. To work most effectively, these agents require a moist wound bed. Chemical debridement includes the use of products such as dextranomers, granular absorbers, and gels that absorb exudate and create a moist wound environment. These products should be selected carefully and used with caution, particularly in grade III and IV pressure sores. Finally, autolytic debridement through the use of occlusive dressings (Duoderm) causes the reduction of eschar formation through the autolytic digestion of necrotic material and creates a moist wound environment for healing. Occlusive dressings provide opportunities for cost control in clinical and home settings by reducing the frequency of dressing changes. Again, they should be used cautiously and changed often in patients with wounds that have excessive moisture to avoid maceration and wound border extension.

Other newer topical products include calcium alginate, a product made from seaweed, to provide a high absorptive capacity and conformability to wounds for healing.[26] The use of topical growth factors to stimulate angiogenesis and promote wound healing is receiving recognition as studies have reported favorable results.[27] These growth factors accelerate wound healing by promoting neovascularization, collagen formation, increased fibroblast and macrophage activity, protein synthesis, and epithelialization.

Behavioral and Educational Management of Pressure Sores

There is a dearth of research examining the behavioral, educational, and psychosocial factors that influence or contribute to pressure sore development. Probably the most cited study is that of Anderson and Andberg.[28] These researchers attempted to determine factors other than physiologic and mechanical that relate to the development of pressure sores in quadriplegic and paraplegic persons. The results of this study showed a strong association between pressure sore incidence and psychosocial variables. A relationship was found between the level of injury and the presence or absence of help with skin care. Probably the most important factor noted in this study was the influence of self-esteem and life satisfaction on a person's feelings about practices and responsibility in skin care. According to Anderson and Andberg, these psychosocial factors were most related to the extent of "persistence"—occurrence, recurrence, and duration—of pressure sores in persons with paraplegia.

While recognizing and responding to the multifactorial nature of pressure sore development in persons with disability, it was through our experience as the rehabilitation component of a regional spinal cord injury program that we identified the need to develop a comprehensive educational-behavioral program for the management of pressure sores. In the early 1980s, a subgroup of our spinal cord-injured population had an 80% recurrence of pressure sores within three months of successful treatment of the pressure sore as an inpatient or outpatient in our Spinal Cord Follow-up Program. This prompted an interdisciplinary team to develop a pressure sore readmission program. The goals of this program include learning specific information and behaviors related to skin care and other aspects of disability management and to define and attain goals related to psychosocial and vocational outcomes. The team recognized that the inci-

dence of recurrent pressure sores was related not only to biomechanical, biochemical, medical, and functional issues but also to psychosocial and vocational ones. As noted by Anderson and others, the ability to initiate, perform, or direct care, the availability of a health care professional, and the knowledge to seek help seemed to have a substantial effect on a person's ability to maintain intact skin and good health.

Our program is based on the premise that a multifaceted approach to educating patients will help alter behaviors to reduce the incidence of recurrent pressure sores. According to the Rosenstock "health belief model," a person's behavior is motivated by the perception of the value and the probability of success.[29] Krouskop also found that a multifaceted program of patient assessment, individualized prescription of equipment, education, and follow-up involving teaching and counseling could reduce the number and severity of pressure sores.[30]

Through the assistance of a coach, a pressure sore program team, and patients already in the program, a new patient learns new skills. The role of the coach is to assist the patient with program participation and completion, to enhance learning and compliance, and to facilitate optimal patient outcomes. The coach meets weekly with the patient, reviews individual and program goals, administers tests before and after program completion and reviews the results, assists with resolving program agreement violations, and monitors the patient's progress and readiness for progression or discharge from the program.

Before entering the program, the patient formally agrees to the goals mutually established by signing a written agreement. The agreement outlines staff responsibilities for assuring program success and the patient's responsibilities for participating in the program. Patients are also informed of hospital policies and procedures, including those related to the use of substances not prescribed by the attending physician. Screening for substance use is done periodically, and a positive urine or serum screen may result in discharge from the inpatient program with ongoing monitoring provided on an as-needed basis in the outpatient follow-up system.

The program has evolved into three phases. Phase I (core) is for patients admitted for the first time with a primary diagnosis of pressure sore (grade II or greater). It is also for persons who previously participated in the program but were unable to complete it, either as a result of agreement violation or acute illness requiring readmission to the hospital. Phase II is designed for persons who successfully complete the program but who are readmitted with another skin problem. Successful completion is defined as a 70% or higher score in the postprogram tests or if a patient shows an adequate knowledge of proper skin care. Phase II classes, titled "Challenge and Enrichment," focus on community and other psychosocial issues as well as on medical-functional and equipment issues. Phase III is a specialized program for patients admitted with a primary diagnosis other than skin breakdown. In this phase, the program team coordinates the rehabilitation components with the educational needs of a person as they relate to the major classes within the core.

The pressure sore program is coordinated through a continuum of care that begins in the outpatient follow-up system. Preprogram screening is done by a physician, nurse clinician, and social worker. The preadmission process focuses on a complete initial assessment with goals and anticipated outcomes mutually developed by the patient and the team. The patient's medical status is evaluated and managed. This includes, but is not limited to, controlling spasticity, treating infection, improving respiratory and nutritional status, evaluating the patient's possible response to pressure sore treatments and interventions, maintaining or improving bowel and bladder status, and addressing functional and homemaker activities. If surgical debridement is indicated, consultation is provided by the program's plastic surgeon. Preoperative education regarding the surgical procedure, postoperative care, and rehabilitation management is provided before hospital admission. Functional and equipment issues are coordinated by a nurse clinician in consultation with a physical or occupational therapist.

The surgical phase (10 to 14 days) involves admission to an acute care hospital. During this admission, the patient is monitored by a follow-up nurse clinician to assure that the acute care team adheres to disability-specific issues, such as bowel, bladder, or spasticity management, and facilitates a timely admission to the rehabilitation phase of the program.

During the rehabilitation phase, the patient actively participates in an individually designed program comprising classes based on program placement, successful testing, or both. The program has expanded to more than 40 possible educational sessions in topics such as skin management, functional-equipment issues, assertiveness classes, and vocational and community survival issues. During this phase the patient is expected to attend a "community" meeting, patient and team meetings, and a coping group. Also during this phase, the goals are to facilitate wound healing, educate, reinforce behavioral skills, and provide a progressive sitting and therapy program directed at maintaining skin integrity.

In an initial unpublished study by LaMantia, the participants of this program demonstrated a positive association between learning, the reinforcement of specific behaviors, and healed skin. According to LaMantia, the "results may indicate that behavioral changes achieved during the program are sustained short term and that certain program elements could act as predictors of success" (unpublished data, July 1986). A follow-up study will be conducted on program participants to assess their ability to sustain behavioral change and to maintain intact skin over time.

During the four years of the program, 131 patients have participated, with 85% requiring only one admission to complete the program.* A second admission was required by 15 (11%) of the 131. This was due to a lack of program completion, agreement violations, or readmission to an acute care hospital because of medical or surgical complications. Four of the patients (3% of the total) have required three admissions to this program, and two patients (1%) required four admissions. Of the 15 persons who required repeated program admissions, 9 (or 7% of the total) have required radical surgical intervention, which included bilateral hip disarticulations, hemipelvectomy, or hemicorporectomy.

The mortality rate among the 131 patients has been 5% (7 patients). The causes of death included pulmonary embolus, respiratory failure, gastrointestinal bleeding, status epilepticus, pyelonephritis with disseminated intravascular coagulation, and pneumonia.

Men made up 78% (102) of the patients. This statistic is

*Data were collected by Carol Goodman, MSN, and Vernice Wooden, MSSA, program coordinators for the Pressure Sore Program, Magee Rehabilitation Hospital, Philadelphia, Pennsylvania.

similar to national distributions of patients with spinal cord injuries, which is often the primary diagnosis of patients participating in this program.

Of the 124 surviving patients, 91, or 73%, have maintained intact skin six months to four years after completing the program. The remaining 27% have had repeated episodes of skin breakdown ranging from grade II to grade IV pressure sores.

Further analysis of those patients requiring readmission is being conducted. This subgroup is similar to the group in the study by Anderson and Andberg. These persons have limited family support or resources, challenging environmental barriers and home situations, limited financial resources, and may also have limited ability or motivation to complete or direct self-care. Although education and behavioral "know-how" have heightened patients' awareness to seek early intervention through the follow-up system, the recurrence of pressure sores in this small number presents a challenge to the patients and the program team.

Of 124 participants, 60 (48%) have returned to a productive life-style, 29 of them returning to school and 31 to a work situation.

The multifaceted approach of this program, combined with a strong focus on patients developing accountability for self-care, has contributed to the successful outcomes experienced by this group.

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REHABILITATION MEDICINE Adding Life to Years

Rehabilitation in Rheumatic Diseases
What's New

MARY L. JURISSON, MD, *Rochester, Minnesota*

In the past decade, considerable change has occurred in concepts of rehabilitation in patients with rheumatic diseases. This includes approaches to functional assessment and outcome, new concepts in exercise, and new orthotics.

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Patients with rheumatic diseases have symptoms that limit their ability to function in daily life: pain, fatigue, decreased range of motion, joint instability, weakness, deconditioning, and depression. Symptoms can often be managed through pharmacologic, physical, surgical, behavioral, and other interventions. Integrating these approaches is essential for the best results. In this article I discuss some of the new developments in nonpharmacologic, nonsurgical interventions.

Assessment and Goal Setting

Rehabilitation focuses on the effect of disease on daily life. In the past decade, attempts have been made to develop, refine, and validate ways of determining problems with function in patients with rheumatic disease.[1-3] These methods specify and quantify disease-imposed limits on patients' ability to move about, care for themselves, work, maintain interpersonal relationships, and enjoy life.

The tools for assessing function vary in the information they seek. Global functional assessment tools for patients with rheumatic diseases, including the Stanford Health Assessment Questionnaire (HAQ), the Arthritis Impact Measurement Scale (AIMS), and others, may show the effect of a rehabilitation program or of drug therapy on the quality of life.[4,5] Other tools such as gait biomechanics laboratory protocols document deficits before and after joint replacement.[6] Functional assessment is a key to deciding the appropriate rehabilitative interventions for specific patients at specific stages in their disease.

Impairments characteristic of various rheumatic diseases (Table 1) can and should be sought in a standard history and physical examination. For example, patients with osteoarthritis have low functional capacity as measured by endurance or aerobic capacity.[7,8] Beals and co-workers showed a decreased maximum work load (525 ± 64 kilo-pond-meters [kpm] per minute versus 575 ± 90 kpm per minute), exercise time (9.5 ± 1.4 minutes versus 11 ± 1.7 minutes), and aerobic capacity (17.8 ± 2.28 $ml \cdot kg^{-1} \cdot min^{-1}$ versus 20.5 ± 2.01 $ml \cdot kg^{-1} \cdot min^{-1}$) in osteoarthritis patients compared with sedentary controls. This probably occurs because as the lower extremity joints become painful with weight bearing, patients decrease the amount of time spent weight bearing and usually do not compensate for this with other conditioning exercises. In taking histories from osteoarthritis patients, questions related to fatigue or stamina may indicate that the patients have become deconditioned.

An evaluation must go beyond the usual functional assessment tools and requires a careful history; physical examination, with attention to joint range of motion, muscle strength, coordination, and stamina; and a neurologic examination.

In patients with more systemic diseases, multiple impairments may contribute to deficits in function. An extreme example is a patient with systemic lupus erythematosus with a history of central nervous system (CNS) insult who also has arthritis. In such a patient, the inability to perform a self-care task, such as putting on a shirt, may result from a combination of problems, including cognitive deficits, a loss in range of motion, weakness of proximal muscles due to chronic

TABLE 1.—*Characteristic Impairments of Rheumatic Diseases*

Rheumatic Disease	*Features That Lead to Disability*
Rheumatoid arthritis	Arthritis (pain, loss of range of motion, joint instability, deformity), muscle weakness, neuropathy, deconditioning, and fatigue
Osteoarthritis	Loss of range of motion, pain, deconditioning, disturbed sleep, and muscle pain
Scleroderma	Arthritis, loss of range of motion, skin tightness, dysesthesia, fatigue (due to deconditioning, cardiac involvement, and pulmonary involvement), and poor nutrition
Systemic lupus erythematosus	Arthritis, stroke, neuropathy, myelopathy, fatigue, myositis, steroid myopathy, pulmonary involvement, cardiac involvement, amputation, avascular necrosis of bone
Polymyositis, dermatomyositis	Myositis, muscle weakness, contracture, pain, arthritis, fatigue, and calcinosis
Fibromyalgia	Fatigue, sleep disturbance, and pain
Osteoporosis	Pain, decreased chest expansion, fatigue, and deconditioning
Seronegative spondyloarthropathies	Arthritis, spinal ankylosis, loss of chest wall motion, deconditioning, and cauda equina syndrome

From the Department of Physical Medicine and Rehabilitation, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
Reprint requests to Mary L. Jurisson, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
kpm = kilo-pond-meter
PACE = People with Arthritis Can Exercise

glucocorticosteroid use, and fatigue due to deconditioning. A single approach may not result in the ability to do the task; improvement in function may require addressing all of these impairments.

In patients with rheumatic diseases involving the CNS, mild cognitive deficits may not be apparent at bedside neurologic testing. Formal neuropsychological testing in patients with lupus has been helpful in following the activity of CNS lupus. Carbotte and Denburg and colleagues found cognitive deficits in 80% of patients who had systemic lupus erythematosus with active or inactive CNS lupus and in 42% of those who "never" had CNS lupus versus 14% of normal controls in formal neuropsychological testing.[9,10] These tests can help identify higher-order cognitive difficulties so that appropriate compensatory behaviors can be taught.

A team approach to rehabilitation is an effective way of assuring a good result.[11] It is important that the members be in fact a team and that many of their roles overlap. For example, a physical therapist and occupational therapist may work together to bring about independent toilet transfers. The occupational therapist will be focused on the role of the upper extremity, which may be deformed or weak and not able to assist well in the transfer. The occupational therapist may make suggestions about the placement of grab bars or the use of adaptive equipment. The physical therapist may work on lower extremity strength and range-of-motion limitations that contribute to the inability to transfer. Working together with a patient may result in success in achieving independent transfers. Table 2 shows the relationship between two problems, the goals, and the interventions.

Exercise

Exercises may vary in performance, intensity, and duration. Several types of exercise and indications for exercise are listed in Table 3. In the past two decades, there have been radical changes from previous approaches to exercise in rheumatic diseases. Before the mid-1970s, patients with rheumatic diseases were advised to rest, and their only exercises were range-of-motion exercises.[12] Although rest plays an important role in the treatment of patients with inflammatory diseases, it became apparent that the deconditioning these patients experienced had a negative effect on their overall function and was a major contributor to their fatigue. Poor endurance is a major factor in their disability. Even patients with rheumatoid arthritis can, however, tolerate aerobic conditioning without serious exacerbation of their arthritis and with substantial gains in their general feeling of well-being, overall strength, and endurance.[7,8,13-16] A surprise benefit of exercise programs may be decreased disease activity. Patients with arthritis tolerate low-impact type training best, including walking, stationary bicycle, and aquatics. Aquatics are tolerated best, but a pool warm enough for arthritis patients (>29°C [84°F]) often is difficult to find. Because of the problem of accessibility, the Arthritis Foundation has developed, in addition to the aquatics program, a land exercise program called PACE (People with Arthritis Can Exercise) and has a videotape of that program for patients who are not in a city that has a group PACE program.

Range-of-motion exercise to maintain and sometimes to regain range of motion is also important. In patients with ankylosing spondylitis, instruction in an exercise program for spinal mobility resulted in improved range and associated improved function.[17] Continuous passive motion machines in the postoperative period after total joint replacement are helpful in rehabilitation. Continuous passive motion may be helpful in resolving cartilage injury.[18] Studies of this in patients with rheumatic diseases have not yet been done.

Strengthening is a more difficult problem in patients with rheumatic diseases because intensive isotonic strengthening can exacerbate the arthritis.[11] Weakness in rheumatic disease patients is a prominent problem and results from inactivity and immobilization, from medications, and from the disease process. Steroid myopathy is an obvious problem in patients receiving high doses of steroids but is notable even at low doses. Danneskiold-Samsøe and Grimby found that rheumatoid arthritis patients receiving glucocorticoid agents had a 30% to 40% decrease in muscle strength and walking speeds compared with similar patients not receiving steroids and that this could impair their ability to use public transportation or cross a street safely.[19] It may be possible to alleviate some of the weakness caused by steroid use. Horber and associates demonstrated that at low doses of steroids, in the range of 20 mg per day or less, transplant patients could achieve normal strength with an isokinetic exercise program.[20] Formal studies of strengthening in patients with inflammatory diseases have not been done. Isometric strengthening exercises in patients with rheumatic diseases have been feasible and effective,[21] but further work needs to be done.

TABLE 2.—*Problems, Goal Setting, and Intervention in Rheumatic Disease*

Problem	*Goals*	*Intervention*
Fatigue	Increase rest	Schedule naps and adequate nocturnal rest period
		Improve quality of sleep with instruction in good sleep hygiene
		Egg-crate mattress surface to improve comfort
		Hot tub bath before bed to decrease pain
	Improve endurance	Low-impact conditioning
	Behavior change	Instruction in energy conservation by occupational therapist
	Identify and treat medical causes of fatigue	Treat chronic obstructive pulmonary disease, congestive heart failure, and inflammation when possible
Knee pain due to osteoarthritis	Pain relief	Analgesics, heat, ice
	Decrease flexion contracture	Heat, range-of-motion exercise
	Regain normal gait mechanics	Isometric and closed-kinetic-chain knee strengthening; gait reeducation
	Decrease stress to knee	Instruction in knee protection and use of a cane

TABLE 3.—*Indication for Several Types of Exercise in Rheumatic Diseases*

Exercise	*Possible Indication*
Rest, relaxation	Pain
Range of motion	Arthritis, immobility
Stretching	Contracture
Strengthening	Weak muscles
Isometric	Arthritis
Isotonic	Strengthening
Isokinetic	Special cases
Closed kinetic chain	Joint instability
Conditioning	Fatigue
Coordination	Apraxia, incoordination
Reeducation	Fibromyalgia, frozen shoulder
Balance	Falls
Posture	Back pain, osteoporosis, ankylosing spondylitis

Exercise in patients with inflammatory myopathy is difficult. There are concerns that vigorous contractions may damage muscle fibers during active inflammation. Traditionally, these patients rest in the acute phase, and only range-of-motion exercises are given to avoid contracture.[22] It is difficult to determine the point at which patients may begin strengthening exercises. Strengthening may best begin when inflammation has subsided with therapy. The report of spontaneous tendon rupture in patients receiving long-term steroid therapy would caution against maximal exercise.[23] Preliminary work suggests that it may be possible for some patients with inflammatory myopathies to exercise even though inflammation is active (J. Hicks, MD, read at the annual meeting of the American Congress of Rehabilitation Medicine/American Academy of Physical Medicine and Rehabilitation, Seattle, Washington, November 1988).

It is easy to design an exercise program that would occupy most of a day for patients with rheumatic disease. This is not feasible for someone who works outside the home and has family obligations. In addition, problems may vary from day to day or week to week, and presumably physical therapy would need to be supervised. To address this issue, new approaches to exercise have included educating patients in exercise principles. This has been successful in the EDUCIZE program developed at Northwestern University (Evanston, Illinois).[24]

Orthotics

Splints and orthotics can be helpful in patients with rheumatic diseases to stabilize unstable joints, to provide pain relief, to allow additional function, and to rest joints.[25] Commonly used orthotics are listed in Table 4.

An addition to this area is the hindfoot orthosis developed at the National Institutes of Health for subtalar discomfort in patients with inflammatory arthritis.[26] This is lighter weight than the standard solid ankle-foot orthosis or patellar tendon-bearing ankle-foot orthosis and allows more mobility than either, while giving excellent pain relief and allowing improved ambulation.

Tripoint finger splints were developed for patients with reducible swan-neck deformities, boutonnière deformities, and distal interphalangeal joint instability. These have been effective in improving function and, in some cases, may be capable of decreasing or reversing deformities. When made from silver or gold, they are much better accepted than the orthoplast materials because they look like jewelry.[27]

Eosinophilia Myalgia Syndrome

The eosinophilia myalgia syndrome is a new syndrome in which eosinophilia, profound myalgias, fasciitis, myositis, peripheral neuropathy, pulmonary fibrosis, sclerodermal skin changes, and other rashes are seen in patients taking certain preparations of tryptophan.[28] This disease has resulted in severe pain from cramping of the muscles and from peripheral neuropathy; profound weakness due to myopathy, neuropathy, and contracture; and fatigue and decreased endurance due to decreased activity, the inflammatory nature of the disease, and poor sleep. On the withdrawal of tryptophan, symptoms may resolve or persist. Varying responses to steroid therapy have been reported; rehabilitation interventions can be helpful.

Most patients get considerable relief of pain and muscle cramping in Hubbard tanks, hot tubs, or showers. Dysesthesias can be managed with heat and, if edema is present, by the use of mechanical edema control measures, such as elevation, decongestive massage, and elastic wraps or support garments. Desensitization massage may further decrease dysesthesia. Occasionally a transcutaneous electrical nerve stimulator may be helpful.

The majority of the contractures are due to skin, subcutaneous tissues, and fascial tightening. Gentle, active range of motion with very gentle end-range stretch in a Hubbard tank can improve contractures. Strong stretching, particularly with rapid movements, seems to stimulate muscle cramping and confound the efforts to improve range of motion in some patients. Mobilizing the skin helps with the contractures, and this can be facilitated by using warm paraffin applied to the distal limbs, hot-water whole-body soaks in Hubbard tanks, or both, accompanied by vigorous soft-tissue mobilization massage.

Strengthening should be deferred until resolution is well under way. Attempts at vigorous strengthening may result in increased weakness, particularly when the movements are rapid, because they seem to stimulate the muscle spasms and disorganized patterns. Progressive, submaximal ambulation programs seem to be the best tolerated. Because of slower reaction times related to stiffness and muscle cramping, patients may need a broader base of support, such as a walker.

Occupational therapy intervention with adaptive equipment, instruction in energy conservation, and work simpli-

TABLE 4.—*Commonly Prescribed Orthotics and Indication in Rheumatic Diseases*

Orthotic	*Indication*
Resting rheumatoid arthritis wrist-hand orthosis	Pain, swelling
Volar wrist support	Wrist pain during activity
Custom	
Prefabricated	
Custom-molded Plastizote shoe inlay with extra-depth shoes	Foot pain
Metatarsal pads or bars	Metatarsophalangeal pain
Hindfoot orthosis	Subtalar pain and instability
Ring splints	Early, reducible swan-neck, boutonnière, and other finger deformities

fication can improve the level of independence in these patients.

Osteoporosis

Osteoporosis occurs involutionally and in association with many rheumatic diseases or the use of glucocorticosteroids. The most difficult problem associated with osteoporosis is fracture of the vertebral bodies, femoral heads, and distal radii. This can be associated with increased dorsal kyphosis and periods of prolonged immobilization. When kyphosis is severe, pulmonary function can be compromised. Evidence points to the importance of axial loading of long bones and vertebral bodies to stimulate new bone formation.[29] Weight-bearing exercise, such as walking, may help maintain axial strength and delay the progression of osteoporosis. Avoiding trunk flexion may notably decrease the frequency of vertebral compression fractures and slow the progress of dorsal kyphosis.[30] The probability of falls in patients at risk can be decreased by maintaining lower extremity strength and agility.

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REHABILITATION MEDICINE Adding Life to Years

Human Immunodeficiency Virus Infection and Diffuse Polyneuropathy

Implications for Rehabilitation Medicine

JON A. MUKAND, MD, *Providence, Rhode Island*

Patients at various stages of human immunodeficiency virus (HIV) infection require rehabilitation services. These patients present problems for each of the disciplines in a rehabilitation team, and all team members must confront the psychosocial and ethical issues involved with the disease. Patients with HIV infection may have polyneuropathy with multisystem involvement, including dysphagia, autonomic dysfunction, respiratory failure, bowel and bladder dysfunction, generalized weakness, a painful sensory neuropathy, and depression. Guidelines are presented for determining if inpatient rehabilitation or other settings are appropriate. Case management is a valuable strategy for the rehabilitation of patients with this complicated disorder.

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The acquired immunodeficiency syndrome (AIDS) has been likened to the Black Death and the influenza pandemic, with good reason. Since the first reports of cases of atypical pneumonia and sarcoma in the early 1980s,[1] 117,800 cases of AIDS have been reported to the Centers for Disease Control as of March 1990.[2] About 1 million people in the United States[2] and between 5 and 10 million people throughout the world are thought to be seropositive for the human immunodeficiency virus (HIV).[3] Projections include 270,000 cases of AIDS in the United States by 1992, of which 172,000 will require medical care.[4]

An increasing number of patients at various stages of infection with HIV will enter the medical system and the field of rehabilitation. Asymptomatic patients may sustain injuries, such as to the spinal cord.[5] In addition, a variety of neurologic complications are related to HIV infection. Physiatrists may see HIV-infected patients for electromyography or pain management, and, finally, general debility associated with AIDS may require rehabilitative services. For each of the disciplines in a rehabilitation team, patients with AIDS present special challenges; all team members must confront the psychosocial and ethical issues involved with AIDS.

In this article I describe a representative case of HIV infection and polyneuropathy in a patient who was treated in a rehabilitation setting, and I discuss implications for rehabilitation medicine.

Report of a Case

The patient, a 29-year-old man with a history of intravenous drug abuse, was admitted with fever, chills, sweats, epigastric pain, adenopathy, and splenomegaly. A year previously he had had lower extremity weakness that resolved spontaneously after a month. Soon after admission he had the development of progressive ascending weakness, a wide-based and unsteady gait, hyporeflexia, lower extremity dysesthesias, dysphagia, and orthostatic hypotension. Because of decreased vital capacity and dyspnea, an endotracheal tube was placed. Electrodiagnostic studies revealed a diffuse polyneuropathy, including prolonged distal latencies of the facial nerve. An HIV test was positive by the Western blot method. Hepatitis B surface antibody and anti-hepatitis A antibody were present. A purified protein derivative test and an anergy panel showed no response. He was placed on a regimen of broad-spectrum antibiotics and transferred for plasmapheresis.

On examination, he was emaciated, febrile, and had tachycardia. Lymphadenopathy and mild hepatosplenomegaly were present. His gag and cough reflexes were diminished, as was facial muscle strength. Strength was grade 2/5 in the upper extremities and 1/5 in the lower, with decreased tone. Sensation was intact to pinprick and proprioception, but light touch was decreased below the ankles and dysesthesias were present in the legs. Deep tendon reflexes were absent.

Because of recurrent fevers, sputum production, and elevated liver function test values, several blood and urine specimens were cultured and a bronchoscopy, bone marrow aspiration, and a liver biopsy were done. The results of all studies were negative or nonspecific. He received numerous courses of antibiotics during his hospital stay, including a course for oxacillin-resistant *Staphylococcus aureus*. The latter infection necessitated isolation procedures, and all therapy was provided with the use of gowns, masks, and gloves.

Methadone maintenance was begun because of his history of drug abuse, and tricyclic antidepressant therapy was started after a psychiatric consultation. The dysesthesias in his legs resolved. A nasogastric tube had been placed because of dysphagia; from a speech pathologist he received thermal stimulation treatments of the oropharynx to help normalize the swallow reflex. A dietician recommended a

From the Medical College of Wisconsin, Milwaukee, and the Boston University School of Medicine, Boston, Massachusetts.

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Reprints not available.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CNS = central nervous system
HIV = human immunodeficiency virus

high-caloric intake because of his hypermetabolic state. Bowel incontinence was a problem initially and was managed with bowel care every other day. A Foley catheter had been placed during the initial management, and this was discontinued when postvoiding residual measuring showed no signs of urinary retention. Extubation was carried out after a month, and the tracheostomy tube was removed after another month; during this time he required frequent respiratory therapy and arterial blood gas monitoring.

Occupational therapy was given to aid in activities of daily living, and adaptive devices were provided. Physical therapy was given to prevent the formation of contractures. Gradually the patient started to ambulate between the parallel bars, then with a walker. A rehabilitation psychologist gave supportive therapy and taught relaxation techniques for the patient's anxiety attacks. A social worker was trying to arrange discharge to a halfway house when, because of psychosocial problems, the patient left the hospital against medical advice.

Discussion

The nervous system is often affected in HIV disease. The virus has been identified in brain, spinal cord, peripheral nerve tissues, and cerebrospinal fluid.[6,7] In addition, antibodies to HIV have been found in cerebrospinal fluid.[8,9] The AIDS dementia complex has been found in 65% of patients with AIDS,[10] with forgetfulness, poor concentration, and slowness of thought the most common symptoms. Behavioral changes such as apathy and depression occur in nearly 40% and are the presenting manifestation in about 20%. Even in asymptomatic seropositive patients, neuropsychological and magnetic resonance imaging abnormalities occur.[11] The course of dementia is progressive over several months to more than a year.[12] Late findings include ataxia, weakness, tremor, myoclonus, seizures, incontinence, and akinetic mutism. The patient in this report may have been affected by the AIDS dementia complex.

Chronic demyelinating and axonal polyneuropathies are the next most common condition, and symptoms are reported by nearly 50% of patients.[13] These consist of weakness, sensory loss, dysesthesias, cranial nerve dysfunction, and autonomic involvement.[14,15] Vacuolar myelopathy can cause ataxia, spastic paresis, incontinence, and posterior column signs, but patients with mild lesions may be asymptomatic.[16] Primary HIV infection may result in acute aseptic meningitis with fever, headache, and cranial nerve signs.[17]

A variety of other neurologic conditions may be diagnosed. Clinical findings besides those mentioned earlier include central nervous system (CNS) toxoplasmosis, cryptococcal meningitis, primary CNS lymphoma, herpes simplex encephalitis, viral myelitis (cytomegalovirus and varicella), candidal brain abscess, progressive multifocal leukoencephalopathy, Kaposi's sarcoma, and metastatic lymphoma.[18] Cerebral granulomatous angiitis,[19] polymyositis,[20] and the Guillain-Barré syndrome[21] have also been reported.

This array of conditions is a challenge to rehabilitation medicine. All manifestations of chronic polyneuropathy were present in this patient, and he required the assistance of all members of the rehabilitation team. Physical therapy should focus on preventing further deterioration. Contractures and muscle wasting can be prevented with active and passive range-of-motion exercises, progressive mobilization with assistive devices, and gait training. Frequent monitoring of vital signs is necessary, especially when a patient has autonomic instability as in this case. Neurodevelopmental training and proprioceptive neuromuscular facilitation may help.[22] Orthotic devices may be required; this patient wore lower extremity splints in bed to prevent contractures and was fitted for an ankle-foot orthosis before he left. Occupational therapy provided the patient with wrist splints to prevent contractures and various adaptive devices to help with activities of daily living. These included a universal cuff for eating; a device to help don socks, a long-handled shoe horn, dressing stick, and button hook for dressing; a long-handled sponge for hygiene; a wedge to build up a pen; a shower chair; a raised toilet seat; and grab bars for the bathroom at home. Occupational therapy can be valuable in maintaining function with adaptive devices, providing therapeutic activities, and teaching energy conservation.[23]

The neurologic effects of AIDS can present a variety of problems for speech pathologists.[24] Because there was a possibility of aspiration pneumonia with this patient, oral intake was initially allowed only under the supervision of a speech pathologist, and the diet was gradually advanced. The dementia complex alone can severely disrupt communication; cranial neuropathies and opportunistic infections affect speech and swallowing; sensorineural hearing losses result from infection of the auditory pathway. In addition, the eardrum can be damaged by Kaposi's sarcoma, herpes zoster, and fungal external otitis. Serous otitis media is common and results in a conductive hearing loss.[24] Nearly half of AIDS patients have a multifactorial hearing loss.[25] Oral manifestations include viral infections such as herpes virus, Epstein-Barr virus, and thrush due to *Candida* species. Hypopharyngeal and laryngeal infections can lead to hoarseness and airway obstruction.[24] These complications have profound implications for speech, swallowing, and nutrition.

Peripheral neuropathies can be caused by HIV infection but can also occur with chemotherapy.[26,27] This patient's dysesthesias resolved with the administration of amitriptyline hydrochloride, but they are often refractory to treatment.[28] Treatment with electrical stimulation and laser therapy, in conjunction with relaxation techniques, has been of benefit.[22] In the terminal stages, pain management is difficult and requires the liberal use of sedatives and analgesics.[29]

Cardiac disease in association with AIDS may determine the exercise prescription in these patients.[30] Kaposi's sarcoma can metastasize to the heart; myocarditis has been associated with cytomegalovirus, cryptococcosis, or toxoplasmosis; and pericarditis can occur with tuberculosis and *Pneumocystis carinii* pneumonia. Congestive cardiomyopathy has been described in the absence of these infections or sarcoma, suggesting a direct effect of the virus on cardiac function. These findings should modify the approach to prescribing exercise in patients with AIDS. The bicycle ergometer has been useful, with progressive-resistance exercises on alternate days. Most patients have resting tachycardia; a target heart rate is obtained by multiplying the difference between maximum and resting pulse by 0.6 and adding the result to the resting rate.[22]

Evidence of *P carinii* pneumonia is found in 85% of patients with AIDS and pulmonary disorders; it can occur with other infections.[31] Many patients also have coexistent Kaposi's sarcoma of the lung. With lung involvement, debilitation is inevitable. Monitoring of vital capacities, incentive spirometry, and chest physical therapy are indicated. Breathing exercises for relaxation and pursed-lip breathing for the fibrosis associated with *P carinii* pneumonia are helpful. Energy conservation techniques maintain functional independence. Strategies for pulmonary rehabilitation in this population are reviewed by Celli.[32] Humidification, bronchodilators, and supplemental oxygen may be necessary. When prescribing exercises, the profound fatigue experienced by these patients must be considered. Physical activity often helps to reduce their stress and helps maintain a level of strength and endurance that allows them to continue performing activities of daily living.

Progressive weight loss is striking in patients with opportunistic infections due to a variety of organisms and sometimes cannot be reversed even with prolonged total parenteral nutrition.[33,34] Severe diarrhea may result in electrolyte imbalances, and hydration must be maintained. The oral and neurologic complications mentioned earlier also interfere with nutrition. The neurologic complications can cause incontinence and require a bowel rehabilitation program. Consultation with a clinical nutritionist can be of great help.

The multitude of neurologic problems described earlier can result in urinary incontinence, as in this patient. Various skin lesions can involve the genitalia, which may further complicate bladder management. Urologic consultation should be obtained.[35] Some patients may require a condom catheter, and others may need indwelling or intermittent catheterization.

The hematologic system is the primary target of HIV infection, and every cell line is affected. Anemia contributes to general wasting. As a result, patients become progressively deconditioned and require the rehabilitative exercises described earlier. Because of platelet abnormalities, bleeding precautions must be observed during these exercises. Lymphopenia and neutropenia contribute to myriad infectious complications; their management in the rehabilitation setting is reviewed by Mayer.[36]

Psychosocial and psychiatric problems invariably occur in these patients. They often face social and emotional isolation because of the stigma of AIDS. Society usually associates the disease with homosexuality and drug abuse, which have their own stigmas. Finally, AIDS is a terminal disease; some patients feel they "deserve" to die and blame themselves,[37] which often leads to depression, anger, and suicide attempts. Clinical presentations can range from mild chronic depression to acute psychosis.[38] Psychiatric consultation is necessary to manage the acute problem and also to help with discharge planning and issues of mental competence. Psychotherapy and group discussions can be helpful.[39] Some patients may require pharmacotherapy, including benzodiazepines for anxiety and antidepressants given at bedtime to help with insomnia.[40] This patient benefited from taking amitriptyline for his depression and also perhaps for his dysesthesias.

Because HIV-related illnesses become chronic, they are similar to the disabilities traditionally treated in rehabilitation medicine. The direct effects of HIV infection and the immunocompromised state often lead to diagnoses commonly seen in the rehabilitation setting. Neurologic conditions such as hemiplegia, quadriplegia, paraplegia, radiculopathies, and diffuse neuropathies can benefit from a comprehensive, interdisciplinary, inpatient rehabilitation program. Musculoskeletal conditions often accompany these neurologic problems but may be the primary diagnosis for some patients with HIV infection. More than 70% of patients with AIDS were found to have rheumatologic involvement ranging from arthralgias to polymyositis, and some would be good candidates for inpatient rehabilitation.[41] Vascular or infectious complications related to HIV infection or to intravenous drug use[42] may lead to amputations. Prosthetists are becoming aware of the subtleties involved in developing artificial limbs for these patients.[43] Pulmonary and cardiac rehabilitation has been useful in a variety of conditions.[44,45] As noted earlier, some aspects of these models have already been used with patients who have HIV infection and have resulted in improved functional capacity and quality of life.

The waxing and waning nature of AIDS is often described as an obstacle to rehabilitation. But the same sort of problem, on a different time scale, is seen with multiple sclerosis. It is true that life expectancy after the diagnosis of multiple sclerosis (mean of 35 years) is greater than the median of 9.8 years for progression from HIV infection to AIDS,[46,47] but, as noted earlier, there is a wide range of survival after the onset of AIDS, and treatments are improving rapidly.

One of the first challenges for rehabilitation medicine is to educate other health-care workers about the potential benefit of rehabilitation. A physiatric consultation should be obtained early in a patient's course, before complications of prolonged bed rest such as deconditioning and contractures occur. The consultation should address transferring the patient to an inpatient unit of the hospital or to a rehabilitation hospital. Criteria for Medicare coverage include the following[48]: "A hospital level of care" is appropriate if a "patient needs a relatively intense program that requires a physician-coordinated multidisciplinary team approach to improve the ability to function." The patient must receive at least three hours a day of physical, occupational, and speech therapy. Some

> degree of mental impairment is not *per se* a basis for concluding that a multidisciplinary team evaluation is not warranted. . . . It is sometimes possible to correct or significantly alleviate both the mental and physical problems.

Patients who are able to go home often benefit from continued rehabilitation services. They may need only an hour of therapy a day, in contrast to the inpatient guidelines of three hours. If a patient is ready for discharge after acute care or after a course of inpatient rehabilitation, staff in physical, occupational, and speech therapy should help ensure the continuity of services through the Visiting Nurse Association. A discharge summary from each of these disciplines will provide guidance to whatever community services are available, including case management programs. The teaching of care givers is also a vital component of discharge planning and may help reduce complications in the outpatient setting. Therapists can do home evaluations to determine if any environmental modifications are needed and help obtain necessary equipment such as wheelchairs and adaptive devices. When funds for purchasing adaptive equipment are not available, as is often the case, various materials can be modified. For instance, a physical therapist reports that foam used as packing material has been improvised for positioning devices

and that friends and family members have sometimes constructed assistive devices for indigent patients (J. Bourgeois, PT, University of Connecticut, oral communication, February 1990). The AIDS Action Committee of Massachusetts rents wheelchairs.[49] Often an initial evaluation at home by physical and occupational therapists can make substantial improvements in the functional status of these patients. The principles of energy conservation and work simplification are vital for preserving their endurance.

When a patient is ready to leave the hospital, a case management system can play a crucial role. Such a system may include assessment, planning, and coordinating a variety of services; monitoring the need for these services, and following up on the patient's medical and psychosocial condition.[50,51] An effective case manager provides the link between hospital and community care and between acute medical and rehabilitative services. Rehabilitation professionals will need to be closely involved in the case management networks that are currently being developed. As noted earlier, rehabilitation involvement in home care is also imperative. This may become more feasible with shifts in public policy. The American Medical Association's Council on Scientific Affairs recently commented that "One new group of home care patients for whom adaptive work strategies and retraining programs are particularly important are patients with AIDS."[52]

Summary

Because of improved treatments, rehabilitation medicine will become more involved in the care of patients with HIV infection. Many disabilities may be associated with HIV infection and require inpatient and outpatient rehabilitation. Funding mechanisms must be developed by government and private payers to pay for the care and rehabilitation of patients with HIV disease.

Health-care workers in rehabilitation medicine need to educate their colleagues and the public about the possible benefits of rehabilitative therapy, not only for patients' quality of life but for society as a whole. Current criteria for the appropriateness of rehabilitation services may be applied to HIV infection; a prognostic system may help select patients for inpatient and outpatient rehabilitation. Case management systems could play a vital role in providing appropriate services. Specialists in rehabilitation medicine should play a role in educating the public and policy makers. Psychosocial issues of health care professionals[53] and their concerns about safety[54] should also be addressed. Finally, there are legal[55] and ethical[56] responsibilities related to rehabilitation medicine and the provision of care in a humane and compassionate manner.

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REHABILITATION MEDICINE Adding Life to Years

Low Vision Rehabilitation

Finding Capable People Behind Damaged Eyeballs

DONALD C. FLETCHER, MD, *Tampa, Florida;* STEVE SHINDELL, PhD, *Atlanta, Geargia; and* TIMOTHY HINDMAN, MA, *and* MARY SCHAFFRATH, OTR/L, *Tampa, Florida*

Loss of vision is a common physical impairment in America today. Comprehensive low vision rehabilitation programs can have dramatic results in increasing the independence and productivity of affected persons. Rehabilitation efforts must be tailored to the type of vision loss and to specific functional implications. Every effort should be made to enhance the residual vision. Activities of daily living, orientation and mobility, and psychological concerns must be addressed.

(Fletcher DC, Shindell S, Hindman T, Schaffrath M: Low vision rehabilitation—Finding capable people behind damaged eyeballs, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:554-556)

Acute eye care focuses on the causes of eye problems, but low vision rehabilitation addresses the consequences. Decreased vision is a problem that affects people, not eyeballs. When nothing more can be done for the macula, optic nerve, or the like, much can still be done for the person. Comprehensive rehabilitation of visually impaired persons can have dramatic results in expanding lives.

Decreased vision is a commonly occurring physical impairment in America. It can occur at any age, but its prevalence increases with age. In the age range of 75 to 84 years, 9.9% of Americans cannot read newsprint using conventional corrective lenses (best correctable visual acuity 20/70 or worse). At ages older than 85 years, the prevalence increases to 25%.[1] Vision loss has been ranked third, behind arthritis and heart disease, among the most common chronic conditions causing a need for assistance in activities of daily living in those older than 70 years.[2(p22)]

Vision loss can cause difficulties as a sole physical impairment or can complicate the rehabilitation process of persons with several impairments. Severe vision impairment was found in 13 (6.8%) of 191 persons admitted consecutively to a rehabilitation unit in New York, making it the fourth most common disability diagnosed.[3]

Types of Low Vision

Low vision refers to a wide range of vision reduction between normal vision and no light perception. Vision loss can be central (reduced visual acuity) or peripheral (reduced field). Common aggravating problems are decreased night vision, slow dark adaptation, reduced contrast sensitivity, and glare.

The most frequent type of vision loss is central, and the most common cause is macular degeneration. Other commonly encountered conditions causing permanent vision impairment are diabetic retinopathy and glaucoma.

Functional Implications of Vision Loss

Those with "normal" vision use it in widely varying ways, and the loss of vision can have widely varying functional implications. These are related to the type of loss, the extent of the loss, the types of activities that were previously engaged in, and the emotional reaction to the loss.

Central vision loss causes difficulties with detail discrimination as in reading books and traffic signs or doing needlework. Field restrictions are usually associated with orientation and mobility problems. The activities that a person has previously made part of his or her life are significant to the effects of vision loss. A mild reduction in central acuity affects a nonreading warehouse laborer who enjoys participating in wrestling and socializing at a beer tavern differently from a jeweler who stops at a library every third day to replenish reading material and plays left field for a baseball team.

Psychological Adjustments

Vision rehabilitation is a biopsychosocial process in which a person's disability, psychological makeup, coping styles, and social environment all combine to determine the potential for adaptation and success. Differences such as congenital or adventitious blindness, partial or total sight loss, and special school placement or mainstreaming can all have a different effect on each person.[4,5] The often-expressed stereotype, however, of people with impaired vision as having a "blind personality" is inappropriate and far from the truth. This stereotype is usually described as consisting of frequent depression, passivity, dependence, chronic anger, and immaturity as a result of adjustment issues relating to the disability and a higher incidence of suicide, substance abuse, and divorce. No study supports this myth. Similarly, the other media image of a young, totally blind man walking with his guide dog to his place of employment, where he then uses braille, talking computers, and other technologic wonders, is a false portrayal of the real world. Most people with impaired vision are elderly women, and the chances of becoming visually impaired increase exponentially in the later years of life. The issues facing an elderly woman with vision impairment and potentially little out-of-home vocational experience and income present several difficult and challenging assessment and clinical problems.

More than two thirds of people with vision impairments

From the Departments of Ophthalmology (Dr Fletcher), Psychology (Dr Shindell), Orientation and Mobility (Mr Hindman), and Occupational Therapy (Ms Schaffrath), University of South Florida, Tampa, Florida, and the Shephard Spinal Rehabilitation Center, Atlanta, Georgia (Dr Shindell).

Reprint requests to Donald C. Fletcher, MD, Medical Center, Box 21, University of South Florida, 12901 Bruce B. Downs Blvd, Tampa, FL 33612-4799.

are older than 65 years. Of those between the ages of 18 and 65, about 70% are unemployed.[6] Of those employed, only 25% work full time.[7] Many disincentives exist that result in people with impaired vision staying unemployed, such as the lack of alternative, affordable medical coverage and long delays reentering the social security system if they lose their job for any reason, including a reduction in sight. Of those who are employed, many are underemployed based on their skills and background because of their lack of vocational mobility compared with nondisabled persons. Given the difficulty of securing employment, many people with impaired vision opt to stay with one employer despite dissatisfaction with pay or advancement. The main problems of people with impaired vision—mobility and communication—necessitate substantial adaptation and commitment to achieve vocational and avocational pursuits.

Psychological adjustment does not have a positive linear relationship with remaining vision. That is, people with partial sight do not have fewer adjustment problems than those totally blind.[8] If anything, research and clinical practice have shown that people with partial disabilities, such as those on crutches and persons with low vision, have more adaptation problems because they present an ambiguous social situation for others. The public simply does not know how to react, and this produces anxiety and the avoidance of anxiety-provoking situations.[9] Thus, many people with low vision find themselves with an ambiguous self-image and may become isolated as friends and family disengage. This may occur because friends and family expect death to follow disability, or it may reflect anxiety over "doing the wrong thing" and upsetting a seemingly "fragile" person with vision impairment. The patients themselves may feel guilty about not "really being disabled" and may resist rehabilitation opportunities offered to them. They may attempt to "pass" as nondisabled to stay employed or to keep from placing too much stress on important relationships in their life; or they may act in the opposite manner, using their remaining vision minimally to decrease expectations or to prepare themselves for a further reduction in sight. To cope with these social situations, it is necessary for persons with impaired vision to gain skills that will enable them to evaluate and take charge of dissipating the anxiety or misconception of others.

Vision loss often follows an unpredictable and somewhat uncontrollable progression. Furthermore, compliance with treatment regimens is often poor. Studies have shown that 75% of patients with treated diabetes mellitus fail to comply with dietary regulations, 50% have poor foot care, 45% perform urine-glucose tests incorrectly,[10] and 80% err in administering insulin.[11] The actual precipitators of the sight loss may have occurred several years before diseases such as diabetic retinopathy began. Diet, exercise, life-style changes, and strict adherence to medical regimens might not reduce or slow the progression of the disease. As a result, patients are often angered by the lack of effective control they have been able to exert on their disease.

Finally, most people with impaired vision are also faced with economic disability. Few have adequate health insurance, and most live below the poverty line. Rehabilitation staff working with people with vision loss need to consider the interaction between patients' loss of vision, their perception of this loss, patients' cultural and social milieus, and the unique functional changes that diminish the quality of life.

Vision Enhancement

Even though vision is substantially reduced, it generally represents the most effective way to obtain information if it can be enhanced. Patients with vision acuity reductions in the range of 20/70 to 20/180 can generally accomplish near-normal reading performance with magnification and optimal lighting. Those with acuities in the range of 20/200 to 20/400 will require strong magnification, and reading will likely be substantially slower than normal. With vision in the 20/500 to 20/1200 range, reading with magnification devices can be accurate but will be slow.

Strong, close-focus spectacles can be useful for reading, writing, and manual chores such as sewing. Handheld and stand magnifiers are also useful for reading print too small to resolve with unaided eyes. Telescopes are useful for clarifying the detail of distant objects such as overhead signs at the supermarket or menus on the wall at a fast-food restaurant. All of these devices come in various strengths and formats that can be tailored to an individual situation. Ophthalmologic or optometric knowledge is necessary for their appropriate prescription.

Special filters can be useful for reducing glare, enhancing contrast, and speeding light-dark adaptation. Various forms of lighting that can be directed on the task at hand and other methods of contrast enhancement can increase the effectiveness of residual vision.

Higher technologic equipment can provide access to printed or electronically stored material in an ever-increasing number of ways. Video magnifiers (closed-circuit television) use a video camera to enhance and magnify material as much as 45 times. For computers, software can enlarge the size of letters on the monitor, or voice synthesizers can speak the words on the screen. Optical character readers can scan pages of text and send them to a computer to have the characters enlarged or spoken.

A key factor common to all vision-enhancing devices and techniques is that considerable practice is required before they are most effective. Having reduced vision and using a low vision device is not at all like reading was before vision loss. For example, patients with macular degeneration frequently have a central scotoma that requires that the object of regard be viewed eccentrically. It is difficult to break the habit of looking directly at the thing one wants to see. The techniques for using low vision devices and changed eyeballs have to be learned, and persistent practice dramatically improves performance. An important part of the rehabilitation program is using the enhanced vision to perform commonly encountered tasks such as paying a bill, balancing a checking account, sorting the mail, rewiring a plug, crocheting, baiting a fish hook, reading a television guide, writing a shopping list, and doing a crossword puzzle.

Activities of Daily Living Adaptations

Vision enhancement devices and techniques must be part of an overall program to rehabilitate the life of a patient, not just the visual system. A prescription for assessment and training by occupational therapy—including consulting with orientation and mobility specialists and rehabilitation teachers—is frequently appropriate.

The overall goal is to recapture, strengthen, and maintain self-confidence for safe, independent functioning. To accomplish this, remaining visual abilities are enhanced, the

usefulness of other senses are demonstrated, and nonoptical and adaptive equipment are used. Existing skills are strengthened, and, when appropriate, new techniques for carrying out activities are introduced. The goals are to strengthen weaknesses to maintain a patient's life-style, not to introduce a new "visually impaired" life-style.

For most tasks of daily living, normal vision provides a surplus of information to carry out the task. After functioning with normal vision for many years, it is not an easy transition to make do with less. Increased attention to more subtle visual clues is necessary; the visual stimulus received is different, and confidence in its correct interpretation must be built. A decreased level of vision will have limitations, but attention needs to be redirected from the unnecessary detail not seen to what is being seen.

Some examples of adaptation equipment and techniques for activities of daily living for persons with impaired vision include large-print reading material, large-button telephones, enlarged checks, felt-tip pens for writing, large-print playing cards, needle threaders, talking watches, and raised-dot markings for oven dials.

Creative problem solving is an important skill for persons with impaired vision. For most of life's activities, there is a way for vision-impaired persons to do them. Visual memory of the task from before the loss of vision guides the present senses through the activity. Every fear must be distinguished from real danger.

Patients are encouraged to approach problems asking, "Is this task difficult or impossible?" If it is impossible, the options to solving the problem must be considered, one of which is to seek assistance from a fully sighted person. A basis for maintaining independence is knowing when help is needed and being willing to ask for it. This gives a person a choice and a sense of control over a situation, decreases frustration, and gets the problem solved.

Conclusion

A macular scar of less than 0.3 mm in diameter can unravel a whole life. Comprehensive low vision rehabilitation can help patients weave together again those tattered threads into a satisfying, full life-style.

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Postpolio Syndrome and Cardiopulmonary Conditioning

RICHARD R. OWEN, MD, *Minneapolis, Minnesota*

Postpolio syndrome is a group of related signs and symptoms occurring in people who had paralytic poliomyelitis years earlier. New weakness, fatigue, poor endurance, pain, reduced mobility, increased breathing difficulty, intolerance to cold, and sleep disturbance in various degrees and expressions make up the syndrome. The reported incidence is between 25% and 80%. The origins are multifactorial and can be associated with underexertion, overexertion, inactivity due to intercurrent illness or injury, hypo-oxygenation, sleep apnea, deconditioning, and the failure of sprouted, compensatory large motor units. The exercise question in postpolio syndrome is related to the experience of new weakness or loss of muscle function due to overuse, which is often associated with injudicious repeated challenges to weakened musculature. Carefully prescribed exercise can be used for increasing strength and endurance and improving cardiopulmonary conditioning.

(Owen RR: Postpolio syndrome and cardiopulmonary conditioning, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:557-558)

Many people who had paralytic poliomyelitis years earlier have been experiencing new problems. In the United States, about 600,000 people have had acute poliomyelitis. A conference in Chicago in 1981 attempted to define the nature, origins, and incidence of new problems associated with the residual or late effects of poliomyelitis.[1] The following related characteristics are often noted: progressive weakness or atrophy, easy fatigability and poor endurance, unexplained pain, additional musculoskeletal disability, reduced mobility, intolerance to cold, increased breathing difficulty, sleep disturbance, and a new neurologic disorder. Various surveys and studies since that conference have indicated an incidence of 25% to 80% in people with residual effects of polio.[2-4] A number of specialized clinics have been established for the purpose of research and management of the postpolio syndrome and its disabling factors.[5]

History

Acute poliomyelitis is a viral disease of the central nervous system resulting in inflammation and damage to areas in the lower brain and spinal cord. The virus enters through the nose and mouth, passes into the bloodstream, and from there into the central nervous system. The primary target of the infection is the motor nerve cells in the spinal cord, but nerve cell damage also occurs in the dorsilateral column and in the brain. The initial attack is characterized by fever, stiff neck and back, tight and painful leg muscles, and scattered areas of paralysis. The virus actively attacks nerve cells for two weeks, but patients may carry the virus for six months after the acute infection.

The paralysis and weakness are greatest at the beginning when swelling occurs in the spinal cord and around the involved nerve cells. Some cells are damaged and some completely destroyed.[6] The muscle fibers supplied by the destroyed nerves atrophy in the absence of control from those motor nerves. Recovery can take one to two years. The process of regaining function may be through the relief of pain and tightness, relearning to use weakened muscles, compensation, and the sprouting of normal cells in the spinal cord to resupply muscle fibers cut off from their nerve fibers.

Many people had "abortive or nonparalytic" poliomyelitis during the epidemic years, some of whom actually had varying degrees of weakness that missed detection initially. Beasly showed that there could be a significant loss of innervation of apparently uninvolved musculature.[7] Wiechers has provided an excellent historical perspective of this condition.[8]

Postpolio Syndrome

The postpolio syndrome presents several problems from the standpoint of research, diagnosis, and management. The disease itself is self-reported. The criteria are related to having had acute poliomyelitis and having new symptoms of fatigue, weakness, pain, breathlessness, and a new disability. There are no satisfactory laboratory procedures to define the origin of the process or the intensity or activity of the progression. Electromyographic studies are useful to identify those who actually had poliomyelitis. Creatine kinase levels have been elevated in about 20% of the people reporting new problems. Many affected persons have contractures or muscle shortening that cause pain and instability at related joints. Many are sedentary, have changed their life activity style, have gained weight, and have abandoned intentional exercise and reduced the level of their incidental exercise. Most have not been involved in an active cardiopulmonary conditioning program. Ventilatory limitations have often imposed further restrictions on activity. Aging compounds the problems by adding to the vulnerability to decay of the sprouted compensatory motor fibers the issue of natural aging of the spinal cord. Intolerance to cold is accentuated, adding the dimensions of pain, swelling, cyanosis, nocturnal cramps, and cold-induced weakness to the syndrome.

Exercise

A major point of contention early in the studies of the postpolio syndrome was the role and risk of activity, exer-

From the Sister Kenny Institute, Minneapolis, Minnesota
Reprint requests to Richard R. Owen, MD, Sister Kenny Institute, 800 E 28th St, Minneapolis, MN 55407.

cise, and rest. A generally accepted view is that the stretching of shortened muscles is beneficial. The work of Knowlton and Bennett showed the potential for injuring overused weakened musculature.[9] Although excesses in unstructured exercise and injudicious activity in the face of weakened muscles is a well-recognized risk, a carefully defined muscle training program can increase strength in selected muscles of persons with the postpolio syndrome.[10-12]

It was a common misconception in our clinic patients that fatiguing daily activity offers a potential for conditioning. Such incidental exercise often challenges the weakest musculature and does not provide an effective training level of aerobic exertion. We were impressed with the poor level of cardiopulmonary conditioning in our initial studies.[13] Adapted cardiopulmonary conditioning was a part of our intital postpolio management protocol.[4] We reported the efficacy and safety of an adapted cardiopulmonary interval training type of aerobic exercise in 1989.[14]

The study had 21 control subjects and 16 exercising subjects. The 6 who dropped out of the exercise group had various conflicts unrelated to the exercise study except for 1 with an abnormal electrocardiogram and 1 with an abnormal blood pressure response. The patients were instructed to exercise three times a week for 15 to 30 minutes using prescribed bouts of 2 to 5 minutes of exercise interspersed with 1 minute of rest. This was to avoid muscle fatigue and the risk of overuse of weakened musculature. Isokinetic muscle testing of peak lift and total work of the quadriceps and hamstrings was done before and after the protocol.

No new weakness developed in response to the training program. All in the exercise group thought that their endurance had improved and fatigue in daily activities had decreased. Most felt that their lower extremity strength had increased. Total work for knee extension was an average of 655.5 ft per lb on the right and 540.7 ft per lb on the left on pretest. After 16 weeks of the study, the exercise group showed an increase on the right to 825.5 ft per lb and 725.8 ft per lb on the left. This represented a 26% improvement on the right and a 34.2% improvement on the left. The study showed that an adapted exercise protocol using an interval training technique increased the maximal oxygen uptake by 15%, increased total work in knee extension by 26% to 34%, and caused no apparent harm.[12] Further studies have been carried out on arm ergometry and measures of exercise, which will be reported later. The arm ergometry showed similarly increased maximal oxygen uptake with no loss of strength.

In the research done on exercise at the Sister Kenny Institute (Minneapolis, Minnesota), there was a high degree of compliance and interest. In the control group, 75% elected to follow the exercise protocol after the first study was completed. No wheelchair athletes had reported to our postpolio clinic in the early years of our program despite there being a large group in our area. Many of them no doubt challenge themselves with activities that tend to maintain a high level of fitness.

Dean and Ross described a modified aerobic walking program that was tested in three patients.[15] They concluded that patients with postpolio symptoms can increase their functional work capacity with a walking program and that the improvement reflects improved biomechanical efficiency as well as training effects. This concept may hold the key to a number of aspects of the postpolio syndrome. Many people describe new weakness that may well represent a loss of an underused or undertrained skill.

Summary

Stretching and flexibility exercises are critical physical hygiene measures for the management of pain, instability, and deformity. These exercises should also precede cardiopulmonary conditioning and other vigorous physical pursuits. Muscle training and strengthening when carefully defined and judiciously implemented can safely build force and power. Resistive exercises should be prescribed for specific goals rather than for purposes of general muscle training. An adapted cardiopulmonary conditioning program has been created to provide improved cardiac status without the risk of overuse damage to nerve and muscle.

The management of postpolio syndrome requires applying traditional physical treatment principles with specific attention to the factors of the vulnerability of compensatory mechanisms to injury by overuse, underuse, underoxygenation, and an inefficient use of weakened musculature. Clinicians must provide information and a balanced prescription of exercise, rest, activity, support, and intelligent accommodation to additional disability.

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Is It All Right to Be Sad?

IRVING KENNETH ZOLA, PhD, *Waltham, Massachusetts*

It was a very hot night . . . not that I needed any excuse. But as soon as dinner was over, I mounted my Stair-o-lator to the second floor and quickly stripped off all my braces. This brought up memories of my mother. Behind closed doors, of course, she would recite the litany of her day and sigh with relief as she stripped off every confining garment from high-heeled shoes to garter belt to girdle. As the sweat poured off me, I matched her item for item and probably sigh for sigh.

Letting my whole body breathe, I stretched out on my high bed, watched the sunset, and grabbed for my latest paperback mystery. I didn't get very far because I could hear Kyra, my 7-year-old daughter, crying in the other room. Ordinarily, that in itself would have caused me to either leap (only figuratively) out of bed or at least call out, "What's the matter?" But I could hear my wife Judy's soothing voice in the background, so I sank back into my reading.

Soon Kyra appeared at the foot of the bed, carrying the ever-comforting panda bear in one hand with the thumb of her other firmly implanted in her mouth, and with tears streaming down her face. I could barely understand a word she was saying, so I reached out and helped her climb up. Words were still not forthcoming, only racking sobs. Holding her close enough so that her tears now were staining my nightshirt, I waited.

"Daddy, I'm so sorry, and I hope you won't think I'm being mean. . . ."

It was such a strange combination—her tears and the supposed meanness—that I didn't really know how to respond or even if I should. So I didn't.

"Daddy," she began haltingly, repeating again her apology. "I know you do so much. I know you do puzzles with me and games and lots of things that Mommy won't do. . . ." The longer the list of my virtues got, the greater became my anxiety. But I had learned over the years with Kyra that with her having such long-winded parents, the last thing she wanted was to be interrupted—especially when she so obviously had a well-rehearsed or rather thought-through prologue.

"It's just"—and out it came, with tears still flowing—"that sometimes I want you to swim out to the dock with me, and sometimes I want you to go bicycling with me, and sometimes I want you to go on long walks with me, and sometimes I want you to climb or go hiking with me. . . ."

As the list continued, I knew that she knew all the things I could do, but that didn't matter. I started to formulate an answer that included a greater use of a motorized wheelchair when she, far wiser than I, said what had to be said.

"You know, Daddy, I asked Mommy if it was OK to talk about something sad even though you can't do anything about it. She said it was and even that it can be good to get it out. Is it really OK?"

As I whispered "Yes," she mumbled through her loud sucking, "I feel better now." "So do I," I said in return as we lay there cuddling.

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From the Department of Sociology, Brandeis University, Waltham, Massachusetts.
Reprint requests to Irving K. Zola, PhD, Mortimer Gryzmish Professor of Human Relations, Department of Sociology, Brandeis University, Waltham, MA 02254-9110.

REHABILITATION MEDICINE Adding Life to Years

Sex and Disability Are Not Mutally Exclusive

Evaluation and Management

GEORGE SZASZ, MD, *Vancouver, British Columbia*

Managing sexual problems in persons with disabilities is a team effort. Physicians have three special roles: identifying problems that are sexual; assessing these problems; and providing psychological, pharmacologic, or surgical treatment methods in the context of the patients' rehabilitation programs.

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Specific information about sexual activity patterns and sexual problems among persons with disabilities is fragmented and incomplete. Existing studies suggest, however, a major decrement in sexual activity in these patients. Humphrey found that only one couple in six remained sexually active after one partner had a cerebrovascular accident in the mid-50s.[1] The reasons given for this included the disruption of the normal rhythm of marital life, side effects of medications, depression in either partner, anxiety in the able partner, physical aversion for the disabled partner, and entrapment in a dependent role.

Almost half of a group of patients with multiple sclerosis indicated that they were sexually "less active" or "not active" since the diagnosis of their illness.[2] About half were concerned about their sexual situation. Men with multiple sclerosis indicated a high frequency of erection, ejaculation, and orgasmic dysfunctions; women indicated a decrease in sexual interest and changes in orgasmic responses.[3,4]

Less than 10% of men with complete injury to the spinal cord can ejaculate.[5] Neither men nor women with complete injury to the spinal cord experience genital orgasms.

More than half of disabled persons participating in a British survey reported that they were currently having problems with sex.[6] Of these respondents, 85% indicated that they would make use of sexual advice and counseling services. In a survey of men with spinal cord injury, 80% of respondents expressed a wish to use the informational or diagnostic services of a fertility clinic.[7] Of respondents to a Sex and Disability Project survey, 90% indicated that they would use sex education or counseling services.[8] In this survey, 64% of respondents expected physicians to provide sex education or counseling services, and 50% ranked the physician as the professional most expected to provide these services.

Physicians need a general strategy for assessing and managing the sexual problems of persons with physical disability.

Identifying Sexual Problems

Table 1 lists a number of functions that, in general, constitute the sexual areas in a person's daily life. Concerns in these areas come to a physician's attention in two ways: the complaints are clearly stated (direct presentation) or information about the problems is elicited by the physician.

Direct Presentation of 'Sexual' Complaints

A woman with multiple sclerosis says that since the last exacerbation of her condition, she has not been able to experience orgasms in intercourse or when masturbating. A man with cerebral palsy complains that he is unable to stimulate himself because he cannot hold his penis in his hands. A 62-year-old woman recovering from a stroke complains that intercourse is now painful. In each of these examples, the patient sought medical help for a "sexual" chief complaint. Sometimes the concerns are expressed through questions: A 32-year-old man with a recent spinal cord injury asked, "Will I be able to satisfy my partner? Will I be able to have satisfaction myself? Will I be able to have children?"

Eliciting Sexual Concerns

The Sex and Disability Project survey indicated that less than 5% of the respondents ever received sex education or counseling services.[8] Many patients are too shy or feel embarrassed to approach their physician with a sexual problem. "Have you any sexual concerns?" is a useful question. Asking a patient, "Do you have any concerns about your genital functioning?" may introduce a series of brief questions about each of the sexual areas listed in Table 1. An informative statement and a question, such as "Many persons with your disability report difficulties with some aspect of their sexual lives. What have been your experiences?" will help to elicit concerns under normal questioning.

Patients may not always be ready to discuss sexual concerns. For example, a physician asked a 19-year-old man with a recent injury to his spinal cord if perhaps he had concerns related to partnership or marriage. The young man said he had no worries in these areas. Several weeks later, however, this man approached the physician again and disclosed that he could not think of any lasting relationship unless it included intercourse. "How can I have intercourse if I don't have erections?" he demanded.

Conducting a Sexual Evaluation

A sexual assessment consists of a history, physical examination, and investigation. Some of the information may have to be supplied by the partner. An attendant may have to help with communication when the patient has a speech disorder. Assistance may be needed also with undressing and dressing before and after the physical examination.

History

The history begins with biographic information. Table 2 lists some of the important background items and their sexual significance. The chief sexual concern is clarified, and the person's functioning in each sexual area is briefly assessed.

From the Sexual Medicine Unit, Department of Psychiatry, University Hospital, Vancouver, British Columbia.
Reprint requests to George Szasz, MD, Sexual Medicine Unit, Department of Psychiatry, University Hospital, Shaughnessy Site, 4500 Oak St, Vancouver, BC, Canada V6H 3N1.

TABLE 1.—*Areas of Sexual Function and Related Problems*

Area	*Expected Functions*	*Problems*
Sexual response	Genital sensation	Altered, absent
	In men	
	Erection	Partial or no erection
	Ejaculation	Delayed, retrograde, absent
	Orgasmic sensation	Delayed, reduced, absent
	In women	
	Lubrication	Diminished, absent
	Vaginal accommodation	Reduced, pain on intercourse
	Orgasmic sensation	Delayed, reduced, absent
Fertility	In men	
	Ejaculation	Retrograde, absent
	Motile spermatozoa	Reduced number, absent
	In women	Physical aspects of pregnancy
Motor functions	Hugging, holding, and other "sex" acts	Unable or lacking skills to carry out "sex" acts
Urinary, bowel, or gas control	Continent during "sex"	Incontinent, wearing stomal pouches, odors
Partnership	Finding partners, maintaining partnership	Inadequate social and courting skills
	Engaging in sex acts	Inadequate or inappropriate "etiquette"
Sexual self-view	Perception of one's "sex appeal"	Anxiety about "performance"
Sexual interest	Desire or motivation for sexual experiences	Reduced, or lack of, interest

The identified symptoms then need to be classified with regard to the duration and circumstance of their occurrence. In terms of duration, the physician needs to find out if the problem is primary, that is, a life-long complaint, or secondary, that is, a relatively recent but persistent complaint that followed a specific event, such as the start of the disability.

In searching for the cause of symptoms in the sexual response area, a physician should keep two principles in mind. First, impairments in genital functioning may or may not be connected to the major disability. A man with spinal cord degeneration said that he was "unable to have intercourse." This inability was first interpreted as an erectile dysfunction secondary to the disability. A more careful review, however, quickly pinpointed the problem: Peyronie's disease (unrelated to the spinal cord degeneration) caused an acute-angle deformity of the man's penis when in the erect state, making intercourse virtually impossible for him.

A 38-year-old woman said that since the onset of her multiple sclerosis, intercourse had become painful. Her problem was first explained as a lack of vaginal lubrication because of her sexual disinterest that in turn was thought to be due to the tiredness associated with her disease. A clarifying history, however, revealed that her pain was only experienced on deep thrusts of the penis. In addition, the woman insisted that her sexual interest had not changed; she merely wished to avoid the painful experiences. A physical examination and ultrasound studies showed a large ovarian cyst that was responsible for the pain on deep thrusting.

A careful history may differentiate between an impairment in genital functioning and a situational dysfunction. In the latter case, a mental state sets in so that a situation generally thought of as "sexual" is reduced to a nonsexual event and hence the person may not experience the expected genital response. A few such nonresponses may be interpreted as failures, which may lead to strong anxieties about the next performance. The anxieties then may precipitate the situational dysfunction. A patient prone to performance anxieties may forewarn the physician of these anxieties by making such comments as, "To me, sex means the act of intercourse . . . oral stimulation or genital stimulation with the hand is foreplay only," or "If I cannot finish because my erection does not last, I don't even want to start it."

Assessing fertility potential. Regular menstrual periods are the best clue to a woman's fertility status. In men, semen analysis is the first step in the assessment. If there is no ejaculation but there is orgasm, retrograde ejaculation must be suspected. The first 20 ml of a postorgasmic urine specimen usually contains the ejaculate.

It is more difficult to assess a person's desire to become a parent. Some persons with severe disability show an overwhelming preoccupation with the issue of parenthood. Assessment questions may need to be aimed at discovering how the couple visualize themselves during the period of pregnancy, birth, the postnatal period, and the first few years of child rearing. Genetic heritage may need to be explored. The intention of all the questions is not to dissuade but to clarify.

Assessing the other sexual function areas. A physician should first try to find out a patient's physical and social

TABLE 2.—*Importance of Background Information*

Item	*Significance of Information*
Age	Advancing age may adversely influence sexual practices
Partnership status	Explains context in which person lives and wants sexual fulfillment
Occupation and education	May indicate person's ability to handle information
Children	Indicates past reproductive and parenting capability
Religious beliefs	May forewarn regarding perspectives to be aware of
Mood levels	Reflects on mental state, may forewarn depression
Nature of the disability	
Congenital	Often implies sheltered life-style
Acquired after puberty	Past partnership and sexual experience likely
Progressive	Recurrent hospital admissions, tiredness
Medical condition	Defines health status; progressive disorders may adversely influence sexual activity
Medications	May have adverse effect on sexual physiology
Past sex practices	Varied and satisfying past practices may be the basis of a future sexual life
Energy level	Sexual interest often depends on energy
Timing of the visit—Why now?	Certain favorable or untoward life events may have occurred recently

TABLE 3.—*Assessing Areas of Sexual Function*

Sexual Function Area	*Relevant Observations and Questions*
Motor functioning capability	Mobility, transfer from wheelchair; ability to dress independently, manual dexterity; hip adduction and knee flexion
Genitourinary and bowel control	Odors, appearance, and cleanliness of stoma bags, urinary conduction devices, leg bags, and catheters
Menstrual control	Extent and regularity of menstrual flow; manual dexterity for inserting tampons
Sexual behavior and partnership	Language skills and social conduct; past partnerships—ages, duration, and depths of relationship; skills of meeting and breaking off; extent of sexual experiences—preference for solitary or homosexual acts
Sexual self-view	Gender identification; manner of dressing, hairdo, makeup, concepts of manliness and womanlinesss, perceived manliness and womanliness, perceived sex appeal and attractiveness
Sexual interest	Compare past and present practice frequencies; efforts made to socialize, efforts made to read sex-oriented books or see sex-oriented movies; dreams and fantasies with sexual content

requirements for finding a partner, maintaining a relationship, creating a private environment, maintaining genital hygiene, or entering into the physical acts of intimate contact and then inquire about the patient's functioning capacity in these areas (Table 3).

Physical Examination

The physician needs to find out a person's physical capabilities as they relate to sexual situations—dressing and undressing, transferring from wheelchair to bed, moving about in a sex act. The general hygiene and cleanliness in the genital area, including the state of stomas and urinary conducting devices, and the structural and neurologic integrity of the genitalia should be assessed.

The first two points can be clarified by observing the patient's way of getting around and by inspecting the genitalia. In men, the genital examination can be done while the patient is in the wheelchair. A pelvic and rectal examination in a person with severe disability may require special arrangements in an outpatient department, where the transfer from a wheelchair to a special examining table might be accomplished more easily and where staff may be available for assisting with leg positioning and the management of leg spasm. Unfortunately, there are no reliable physical tests to show the capability of erection. In men with spinal cord injury above the sacral neurologic levels, physical touch to the penis may cause a reflex erection. Sometimes these erections prove to be sufficient for the act of intercourse, but often they last for only a few seconds. If there is evidence of a low spinal cord lesion and a squeeze of the testicles produces pain, erection in response to mental stimulation may be possible. These penile reactions are often insufficient for intercourse.

The potential for orgasmic responses in men and women with neurologic lesions is usually confirmed when patients correctly identify a pinprick sensation on the glans penis and in the clitoral area and are able to contract the anal sphincters voluntarily (or "wiggle" the penis and contract the vaginal os). The former test confirms the integrity of the lateral spinothalamic tracts, the latter that of the continuity of the pyramidal tract system. These two spinal cord tracts seem to be essential for the occurrence of orgasmic reactions.

Investigations

The simplest way to investigate sexual problems is to ask people to experiment privately and then report their findings.

Measuring nocturnal penile tumescence may be of value when information from the history is insufficient to differentiate between a situational (psychological) and a global (organic) erectile dysfunction.[9] A satisfactory response to an intracavernous injection of papaverine hydrochloride or prostaglandin E_1 usually eliminates a vascular cause in a patient with erectile dysfunction. An unsatisfactory response to even higher dosages of these medications suggests a vascular origin requiring further investigations.

Urodynamic tests may be useful for estimating the integrity of the urinary system and, indirectly, the neurologic integrity of the erectile or ejaculatory responses.

Laboratory tests may include serum testosterone levels and sex hormone-binding globulin ratios in men, estrogen and progesterone levels in women, and luteinizing hormone, follicle-stimulating hormone, and prolactin levels in both.

Providing Care

One consideration in treatment is that a patient is not a "disabled" entity but a person who has a desire for adequate interpersonal and sexual functions and who happens to have certain disabilities. The other is that the management of sexual problems may be incomplete without attention to the patient's psychological, social, and vocational rehabilitation.

Direct and Indirect Care

Direct care may include listening to a person with a sexual concern, giving information about sex physiology or practices, offering suggestions about adapting physical activity techniques of daily living to the physical demands of intimate physical contact, and providing in-depth management.

Indirect care may consist of providing opportunities for privacy and making arrangements for social occasions and the needed transportation. Physicians and other health or social care professionals, partners, and friends, regardless of role or job title, can provide many aspects of indirect sexual health care. The facilitation of social skills, such as language skill management and improving appearance through appropriate dressing, hair care, or cosmetics, is important.

Most persons with disability and a sexual problem expect a physician to assist with concerns related to genital functioning, fertility, and dilemmas in selecting the appropriate birth-control method.

Treatment of Sexual Response Problems

Talk-oriented methods. Sex therapy was originally designed for nondisabled, highly motivated couples when one or both partners suffered from psychologically based erection and ejaculation problems in men and orgasmic problems and pain on intercourse in women. An advantage of this technique, however, is that it can be applied in steps. For example, in couples for whom intercourse is not a realistic possibility either because of physical limitations or because of impairments of genital functioning, specific suggestions can be offered about experiencing erotic pleasure without concern for erection, erection without orgasm, extravaginal orgasm, or intromission without orgasm.[10] Persons with spinal cord injury, for example, often report pleasurable sensory

experiences arising out of caressing the ear, neck, or other areas of the body where sensory perception has been spared.

Pharmacologic methods. Intracavernous self-injections of papaverine hydrochloride, papaverine and phentolamine mesylate, or prostaglandin E_1 may assist erectile problems. An evaluation of the short-term and long-term consequences of this method may be found elsewhere.[11,12] Patients must have either a reasonable degree of eye-hand coordination and manual dexterity to self-administer the injections or a partner who is willing to give the injections. Persons with neurologic impairment of the erection process are particularly prone to medication-induced priapism and require a considerably smaller dose than do others. Women in their postmenopausal years may require hormone supplementation to prevent pain on intercourse.

Surgical methods. Penile prosthesis implantation may be of value for men with organic erectile dysfunction. This approach, however, in addition to its recognized disadvantages, may impose further problems on a person with spinal cord injury. The prosthetic device may cause pressure sores in men with neurologic injury. Hand dexterity is required to activate some of the devices. Use of the device may interfere with urinating.

Assisting with physical methods. Intimacy does not require sexual intercourse. Virtually no disability precludes some form of physical closeness in bed. A partner may assume responsibility for body positioning. The loss of arm, hand, or finger dexterity may be compensated for by the mouth. A vibrator may be useful in self or partner stimulation. Physiotherapy techniques used to improve capabilities for performing activities of daily living can be used to improve the ability for sex practices.[13] External prosthetic devices may provide a noninvasive method of inducing erection. Some of these devices are condom-shaped and use a vacuum principle to stay on a flaccid penis. This method may be of additional value to persons who are concerned about urinary incontinence during intercourse. Other vacuum principle-based devices use a strong rubber band to hold the venous congestion in the penis.

Treatment of Fertility and Birth Control Issues

New techniques are becoming available for procuring sperm. This is particularly important for younger persons with spinal cord damage who have neurologic impairment of the ejaculation mechanism. Vibratory stimulation of the penis and electroejaculation techniques are proving to be the two most useful methods when followed by artificial insemination procedures.[14,15] Many men with severe disability are able to ejaculate but may not be able to perform the act of intercourse. Their ejaculate may be collected in a nonspermicidal condom and transferred into the vagina by a physician or at home by the nondisabled partner. Persons with certain disabilities may require genetic counseling before considering fertilization procedures.

Most birth-control methods pose disadvantages to persons with a disability. Each method needs to be thought of as either active (for example, putting on condoms, inserting a diaphragm) or passive (for example, using an intrauterine device, taking birth-control pills, or having a vasectomy or tubal ligation).[16] The active methods require a certain degree of motor coordination. Of the passive methods, an intrauterine device may be troublesome to women with sensory deficiencies because they may not be able to feel symptoms of uterine perforation. Birth-control medication may be contraindicated for women in wheelchairs, who may have a predisposition for thrombophlebitis.

Managing menstrual hygiene in women with severe disability may require suppressing ovulation or doing a hysterectomy. Women with disabilities must have a clear understanding of the implications of a hysterectomy.

Outcome of Care

The complexity, urgency, depth, and variety of needs, goals, and experiences in the sexual areas are highly personal and may vary with such factors as age, gender, physical ability, or health status. Two persons with a seemingly similar disability and about the same medical approach to their sexual problems may end up with different results. My experience with persons with spinal cord injury suggests that, regardless of the severity of the disability, the prognosis is good for reestablishing or creating a satisfactory (although perhaps different) sexual life-style when patients' past sexual experiences were varied and satisfying and when there exists a relationship with a sexually interested and interesting partner.[17] The physician's inquiry and appropriate assessment confirm a patient's manhood or womanhood. This confirmation seems to be an important component of the rehabilitation process.

Summary

The key to a physician's success in assessing and treating sexual problems is comfort in asking relevant questions. In turn, comfort comes from two sources: accepting disabled patients as persons, who happen to have certain disabilities and whose sexual needs, goals, and experiences are similar to those of the seemingly nondisabled; and using a framework to guide an objective assessment. Once the needs and goals are clarified, decisions can be made rationally about providing the appropriate medical assistance.

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"The greatest discovery of my generation is that human beings can alter their lives by altering their attitudes."

WILLIAM JAMES

"Nothing is impossible: there are ways which lead to every thing; and if we had sufficient will we should always have sufficient means."

FRANÇOIS ROCHEFOUCAULD

"The world is moving so fast these days that the man who says it can't be done is generally interrupted by someone doing it."

HARRY EMERSON FOSDICK

"A true friend is one soul in two bodies."

ARISTOTLE

"Life is action and passion. It is expected of a man that he share in the action and passion of his time under penalty of being judged not to have lived!"

OLIVER WENDELL HOLMES

Rehabilitation of Severely Injured Children

BRUCE M. GANS, MD, *Detroit, Michigan, and* CARLA DI SCALA, PhD, *Boston, Massachusetts*

Injury is the leading cause of death and disability in childhood. Ideal systems of care integrate comprehensive management of acutely injured children with rehabilitation. We review the nature of childhood injury, its disabling consequences, and the best ways to manage the care of children with serious injuries.

(Gans BM, DiScala C: Rehabilitation of severely injured children, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:566-568)

Acutely and severely injured children are frequently in need of rehabilitation services and programs. They may need a single service, such as specific exercises provided by a physical or occupational therapist, or diagnostic assistance by a physiatrist, such as an electrodiagnostic examination to determine prognosis in a nerve laceration, or they may need more extensive help, requiring a comprehensive multidisciplinary rehabilitation program.

Nature of Disabling Childhood Injuries

The full nature and scope of childhood injuries is becoming better understood through a major multi-institutional study called the National Pediatric Trauma Registry.[1] Centered at Tufts-New England Medical Center in Boston, Massachusetts, the registry collects information from 55 pediatric trauma centers in the United States and Canada. Funded by the National Institute on Disability and Rehabilitation Research, the registry has a unique focus on the functional status of surviving children discharged from acute care.[2] Phase I of the study, conducted from 1984 to 1988, contains the case records of almost 12,000 children. Phase II (in operation since the close of Phase I) contains an expanded information set about functional status and currently holds more than 10,000 records.

In the data set, nine specific domains of function are identified, including vision, hearing, speech, self-feeding, bathing, dressing, walking, cognition, and behavior.[3] Each function is rated as to age-appropriate or disabled. In the Phase II data, estimates of the duration of the disability are also made by the discharging trauma center.

The combined data set of almost 23,000 records reveals a number of important demographic characteristics about childhood injury and the associated impairment, disability, and handicap. For the entire 23,000 cases, 66% are male. Approximately 97% of the children survived their injuries and were discharged from the trauma center.[4] About 4% of the disabled children were transferred to inpatient rehabilitation programs.

Figures 1 through 8 show the data that resulted from this study.[1,5] From these data, it is clear that childhood injury requires a variety of rehabilitation services and programs and that multisystem injuries, extremity injuries, and traumatic head and neck injuries are the dominant diagnostic groups in need of services.

Comprehensive Care of Injured Children

The best system of care for an injured child includes early and effective rehabilitation services. A Level 1 pediatric trauma center will have a pediatric physiatrist available 24 hours a day to help initiate this care. In the earliest phases of management, an injured child's life may be in jeopardy. A rehabilitation team will be able to focus on less life-threatening aspects of care that will allow surgeons to better manage the primary injury. If the rehabilitation team institutes preventive care for contractures and skin breakdown, for example, many problems will be avoided.

In serious injuries, participation by the rehabilitation team in medical and surgical decision making will lead to the best outcome. In a patient with a crushed limb, for example, the rehabilitation perspective on the functional options for elective amputation can be important in determining the level of amputation. Similarly, in patients with spinal fractures, orthopedic surgeons, neurosurgeons, and physiatrists may jointly make decisions that allow the fastest recovery of mobility.

Early referral to a rehabilitation team will allow func-

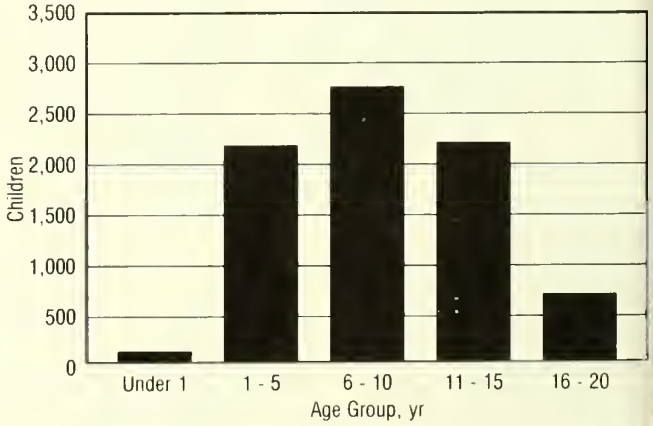

Figure 1.—Age distribution is shown of injured children with residual disability (from the National Pediatric Trauma Registry Phase I and Phase II data, 8,642 cases).

From the Department of Physical Medicine and Rehabilitation, Wayne State University School of Medicine, Detroit, Michigan (Dr Gans), and the Department of Rehabilitation Medicine, Tufts University School of Medicine, Boston, Massachusetts (Dr DiScala).

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Reprint requests to Bruce M. Gans, MD, Rehabilitation Institute of Michigan, 261 Mack Blvd, Detroit, MI 48201.

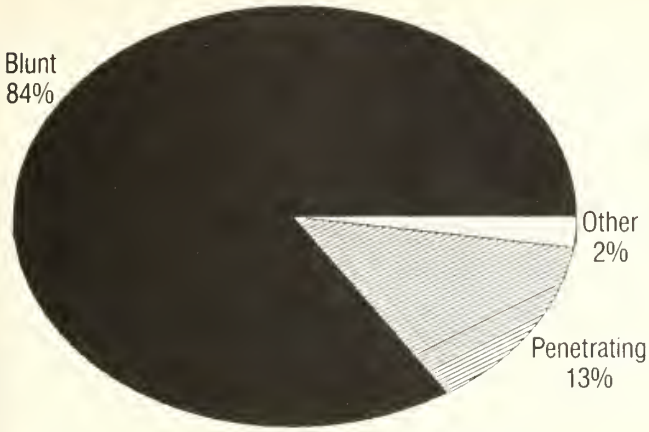

Figure 2.—The "pie" is divided into the type of injury experienced by children with residual disability (from the National Pediatric Trauma Registry Phase I and Phase II data, 8,642 cases). Blunt injury is the dominant type of injury experienced by this population.

tional considerations to be integrated into the acute care plan, responsibility for certain aspects of care to be delegated, and the various specialists in a patient's care to participate fully in decision making so that priorities can be established for patient care and resource allocations.

Injured children who will benefit most from early rehabilitation referral include those with traumatic brain injury, spinal cord injury, multiple bone fractures, major neurologic injuries of the peripheral nervous system, and traumatic amputations. Children with paralysis, spasticity, loss of sensation, contractures, decubitus ulcers, and multifactorial impairments will likely benefit symptomatically from a timely referral.

The disabilities that should be addressed by a rehabilitation team include disruptions of communication, mobility, self-care skills, cognitive function, schooling, and the ability to play. A patient with any combination of dysfunctions should be strongly considered for referral.

Specific Rehabilitation Problems

Communication

For children with serious disruptions of communication abilities, such as those due to airway diversion or brain injury, providing alternative methods of communication should receive the highest priority, whether through the use of writing, signing, or lip reading. For those few children with residual motor or neurologic deficits, the use of augmentative communication systems and devices such as speech-generating computer systems may be necessary.

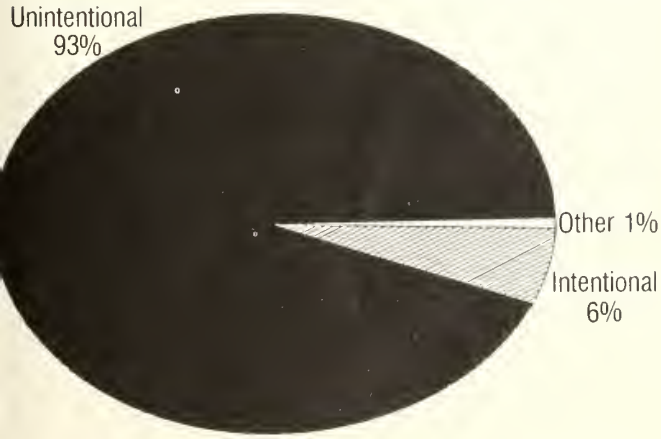

Figure 3.—The circumstances of injury experienced by children with residual disability are shown (from the National Pediatric Trauma Registry Phase I and Phase II data, 8,642 cases). Most children in this study are the victims of unintentional injury.

Mobility

Early in almost any serious injury, mobility will be limited. For those children who will not quickly return to walking, the use of a manual or powered wheelchair will be required. Many specialized wheelchairs now exist for children, including lightweight manual chairs and developmentally appropriate power wheelchair systems. Prescribing appropriate seating and positioning systems for the wheelchair and other environments will also be important for long-term rehabilitative management.

Self-care

The reestablishment of preinjury self-care skills is important. Temporary impairments, such as those requiring upper extremity casts, may make accommodating to dependence preferable to major therapeutic interventions. On the other hand, a severely impaired child will require long-term and developmentally gauged therapy services to learn either new methods or to use adaptive aids and devices to achieve independence.

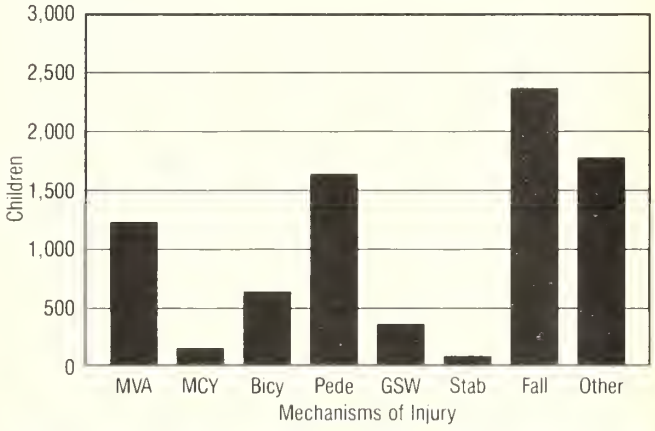

Figure 4.—The mechanisms of injury are shown for children with residual disability (from the National Pediatric Trauma Registry Phase I and Phase II data, 8,642 cases). Bicy = bicycle, Fall = fall from height, GSW = gunshot wound, MCY = motorcycle, MVA = motor vehicle accident, Pede = pedestrian-vehicle injury, Stab = stabbing. Vehicle-related injuries account for 44.7% of all cases.

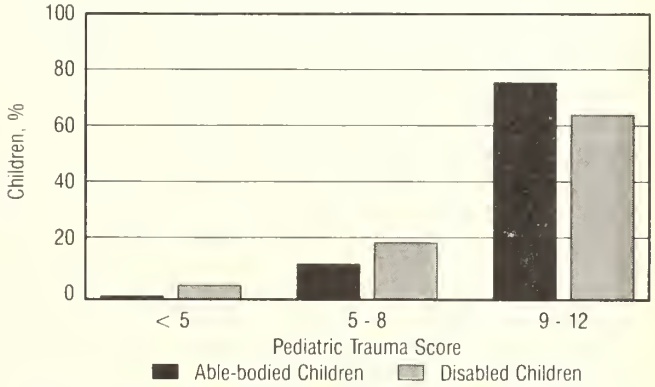

Figure 5.—A Pediatric Trauma Score (PTS) is recorded for injured children (from the National Pediatric Trauma Registry Phase I and Phase II data—12,263 able-bodied cases and 8,333 disabled cases—and Tepas et al[5]). The lower the score, the more life-threatening and severe the injury. Children with lower PTS ratings are more likely to have disability from their injuries.

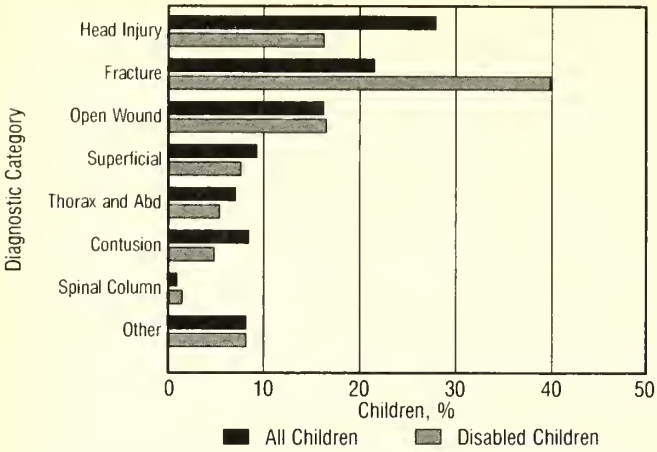

Figure 6.—The diagnostic category is shown for all injured children and those with residual disability (from the National Pediatric Trauma Registry Phase I and Phase II data; 22,508 total cases, 8,642 disabled cases). "Head Injury" includes skull fractures, concussions, and intracranial injuries; "Fracture" includes all noncranial fractures; "Open Wound" includes all lacerations and amputations; "Superficial" includes abrasions; "Thorax and Abd" includes all injuries to internal organs of the thorax and abdomen; "Contusion" includes superficial injuries with intact surface; "Spinal Column" includes all injuries to the spinal column, with or without neurologic involvement; "Other" includes strains, injuries to blood vessels or nerves, and the like.

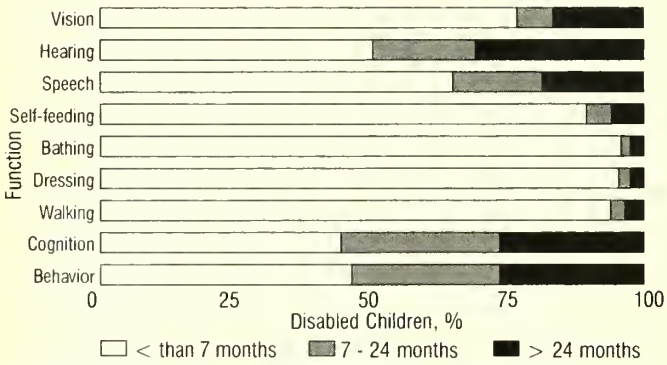

Figure 7.—The graph shows the duration of disability. The anticipated duration in 1 or more of the 9 categories of function is assessed by the trauma center at the time of discharge (from the National Pediatric Trauma Registry Phase II data only, 4,041 cases).

The Ideal System of Health Care

An ideal system of trauma care recognizes the desirability of early and effective integration of rehabilitation services into the acute care system. A screening evaluation by a physiatrist or other rehabilitation team member will be necessary. Standing protocols for making decisions and developing comprehensive care plans will be in place. A trauma center

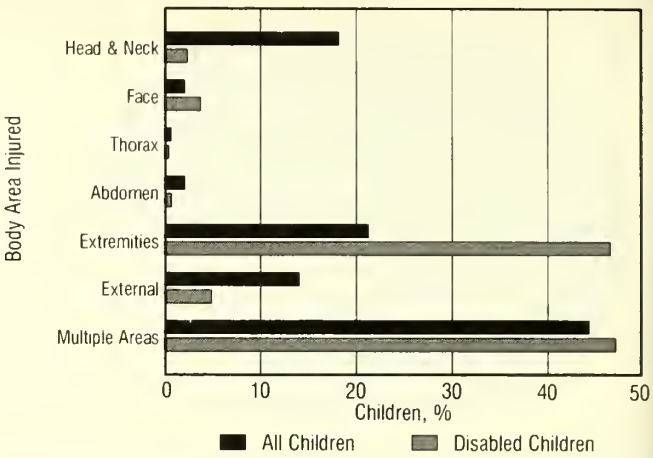

Figure 8.—The graph shows the injured body area (from the National Pediatric Trauma Registry Phase II data, 4,041 cases). Multilocation injuries, extremity injuries, and head, face, and neck injuries are more commonly associated with residual disability.

with a comprehensive rehabilitation program is likely to have a "seamless" interface between the acute and rehabilitative systems.[3]

As a patient-centered system of care, the ideal pediatric trauma system will be concerned not only about the survival of its patients but about their long-term ability to function. This will result in a program that monitors its performance and documents long-term follow-up with standardized data collection and periodic program reviews.

Conclusions

The rehabilitative care of injured children is an important aspect of any pediatric trauma system. Because almost all children who are admitted to a trauma center will survive, impairments and disabilities should be of the greatest concern. By prospectively incorporating a comprehensive rehabilitation program into an acute care system, resources will be used most effectively and the best results will be achieved.

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REHABILITATION MEDICINE Adding Life to Years

Rehabilitation in Cerebral Palsy

GABRIELLA E. MOLNAR, MD, *Oakland, California*

Cerebral palsy is the most frequent physical disability of childhood onset. Over the past four decades, prevalence has remained remarkably constant at 2 to 3 per 1,000 live births in industrialized countries. In this article I concentrate on the rehabilitation and outcome of patients with cerebral palsy. The epidemiologic, pathogenetic, and diagnostic aspects are highlighted briefly as they pertain to the planning and implementation of the rehabilitation process.

(Molnar GE: Rehabilitation in cerebral palsy, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:569-572)

The clinical syndromes of cerebral palsy share three unifying diagnostic criteria: The leading symptom is a *movement disorder* resulting from *nonprogressive brain damage* that has affected the *immature central nervous system.*[1] The possibility of deficits in areas other than motor function is implicit in the underlying disorder. According to this definition, the time of brain damage may be prenatal, perinatal, or postnatal. Most cases are related to prenatal or perinatal antecedents or both.[1-3] Several large-scale studies indicate that in both term and preterm infants, prenatal factors have a more significant role than was previously recognized.[1-4]

In premature infants, the risk of cerebral palsy is inversely related to birth weight. A residual motor deficit following a central nervous system injury or illness sustained between 4 weeks and 5 years of age can be classified as postnatal cerebral palsy after the acute stage has passed.[1] Postnatal causes are responsible for 10% to 15% of cases. No cause is apparent in 20% to 30% of cases wherein symptoms occur early.[1]

Classification

The classification of cerebral palsy is based on the clinical signs of motor dysfunction.[1] Spasticity is the presenting sign in most cases (Table 1). Diplegia is the accepted classification when the lower extremities are affected and usually follows hemorrhagic or hypoxic periventricular lesions of prematurity.[2] As a rule, in quadriparetic distribution of spasticity there is a greater impairment of the legs. By convention, double hemiplegia designates quadriparesis with more involvement of the arms. Dyskinetic clinical types include several movement disorders; athetosis and dystonia are the most common. Preventive treatment of neonatal isoimmunization and bilirubin encephalopathy has reduced the occurrence of typical kernicteric athetosis and the relative frequency of dyskinetic cerebral palsy in general.[5] Other clinical types represent a small number of cases with predominant or mixed signs of various movement abnormalities. The possibility of familial and progressive neurologic disease must be ruled out when ataxia with or without spasticity is the leading sign.[1]

TABLE 1.—*Clinical Classification of Cerebral Palsy*

Clinical Type	*Relative Frequency, %*
Spasticity	75-85
Hemiparesis	10-15
Diplegia	35-40
Quadriparesis	25-30
Dyskinesia	5-10
Athetosis	5-8
Dystonia	2-3
Choreiform, ballistic, tremor	Rare
Other types	10-15
Spastic, athetoid	5-10
Rigid, spastic	3-5
Ataxic diplegia	Rare
Ataxia	Rare
Atonia (hypotonia)	Rare

Diagnosis

The early detection of cerebral palsy has some diagnostic uncertainties. Several independent long-term studies have shown that initial neurologic abnormalities may resolve and have demonstrated the need for caution about unjustified labeling of young infants as having cerebral palsy.[1,6,7] On the other hand, definitive signs sometimes do not become evident until volitional movement control begins to emerge. A suspicion of cerebral palsy is usually confirmed during the second half of the first year. Mild cases with subtle symptoms, however, may escape detection until the second year when delayed or abnormal standing and walking become noticeable.[8]

Signs and symptoms that should arouse suspicion are abnormalities of tone, posture, and infantile reflexes, delayed motor development, and atypical motor performance.[9] Hypotonia is a precursor of spasticity or athetosis. A long-standing hypotonic stage or definite spastic hypertonicity around the age of 6 months suggests a severe motor deficit. A fisted hand with thumb adduction, scissoring of the legs, and a tendency for opisthotonus are typical postural deviations. Persistent Moro and obligatory tonic neck reflexes are examples of infantile reflex abnormalities. Late sitting is often the first symptom of parental concern. Motor delay tends to increase with successive milestones. Hand preference during the first year is an indication of impaired coordination of the contralateral arm in hemiparesis. Crawling in a prone position rather than on hands and knees or toe walking are well-known signs of motor deficit in the lower limbs.

From the Department of Pediatric Rehabilitation, Children's Hospital Medical Center, Oakland, California, and the Department of Physical Medicine and Rehabilitation, University of California, Davis, School of Medicine, Davis.

Reprint requests to Gabriella E. Molnar, MD, Department of Pediatric Rehabilitation, Children's Hospital Medical Center, 747 52nd St, Oakland, CA 94609.

TABLE 2.—*Disabilities Associated With Cerebral Palsy*

Type	*Estimated Frequency, %*	*Clinical Types With Highest Relative Frequency*
Dysarthria	20-30	Athetosis Spastic quadriparesis
Visual deficits Strabismus Hemianopsia Refractory errors Decreased visual acuity Blindness	60	Spastic diplegia Spastic quadriparesis Spastic hemiparesis Spastic/dyskinetic (2:1)
Hearing impairment Sensorineural	25-30	Athetosis (kernicterus 75%; other 25%)
Mental retardation	50	Atonic and rigid types Spastic quadriparesis
Perceptual dysfunction Learning disability	40-50	

Rehabilitation

The rehabilitation of children with cerebral palsy requires a developmentally oriented approach that is not limited to the care of the motor disorder.[10] The therapeutic team consists of the family, physicians, and other contributing professionals who must have a clear understanding of attainable goals. Taking advantage of functional assets, promoting compensatory adaptations, and preventing the secondary consequences of disability are principles of rehabilitation that are distinguished in concept but inseparable in practice. Changing concerns from childhood to adult life call for adjustments in treatment and priorities.

In addition to a movement disorder, other functional deficits may reflect central nervous system damage.[5] Table 2 shows the estimated overall rate of associated disabilities and their relative frequency in different clinical types. Comprehensive rehabilitation entails assessing all aspects of function and appropriate remediation.

Motor Disability

Early intervention programs address developmental deviations that result from associated central nervous system deficits or are imposed by impaired motor function.[9] Public Law 99-457 (Education of the Handicapped Act of 1986) is a federal mandate to provide such programs for high-risk infants.

Therapies for neuromuscular disorders in infants and young children incorporate handling, positioning, and play to challenge postural and movement responses that are prerequisites for gross and fine motor milestones. Feeding difficulties require the facilitation of oral motor coordination to improve swallowing.[11] Instructing the family in modified ways of physical handling extends therapeutic efforts to everyday activities at home.[11,12] Therapy becomes more structured as children learn to follow instructions and are able to cooperate. During the preschool years, the functional goal is to achieve the most effective mode of locomotion and self-care skills, with assistive devices if necessary.

Physical therapy is a widely used treatment method. Among the techniques proposed for patients with cerebral palsy, some remain controversial on both theoretic and clinical grounds.[11,13,14] Controlled trials on the effectiveness or comparative efficacy of various techniques are scarce.[15] The great diversity in physical and associated deficits and in the consequent natural course poses difficulties for designing research studies. Clinical experience indicates that no therapeutic method can produce striking changes in the functional potential determined by a central nervous system deficit. The contribution of physical therapy is to ameliorate the adverse effects of disuse, inexperience, and secondary complications. The importance of these benefits, however, should not be underestimated.

Compensatory functional training includes a range of rehabilitation possibilities that can be illustrated by several examples. Environmental modifications to ensure access, suitable clothing, and learning to use simple adapted implements for feeding, writing, and other daily tasks are practical approaches to independence that occupational therapy offers.[5,12,16] Although assistive devices such as crutches, walkerettes, and wheelchairs have been used for a long time, rehabilitation engineering has revolutionized the technology for disabled persons. The light weight and versatility of new wheelchair designs allow greater mobility, including participation in adapted sports. An important development for patients with cerebral palsy is the construction of wheelchair seats that incorporate biomechanical features to alleviate abnormal tone and posture.[5,9,17] When upper extremity impairment necessitates, motorized wheelchair models are available from pediatric to adult sizes. Children with adequate cognitive, visual, and spatial discrimination abilities can learn to operate a motorized device under adult supervision as early as 3 years of age. Electronic and computer technologies have created a range of possibilities to help patients overcome physical restrictions in activities of daily living, education, work, and leisure.[9,17] Economic constraints are the primary obstacle that limits the availability of such devices.

Preventing musculoskeletal complications, which can further compromise function, constitutes an additional aim of treatment.[9] Abnormal tone, movements, and posture create a risk of soft tissue contractures and bone deformities. The propensity for these complications is greatest during the rapid phases of growth in childhood, but an insidious progression may continue after skeletal maturity.[18] Anticipatory treatment is the best preventive measure. Options include range-of-motion exercises, splinting, braces, and surgical procedures as warranted by the clinical findings and course.

Therapy is most intensive from infancy to early school years because most children reach their expected functional capacity in ambulation and daily activity skills by school age.[19,20] As formal therapy is gradually tapered, consistent practice at home and school and in other functional situations must continue to increase motor proficiency, endurance, and the self-initiated acquisition of new skills. Adapted physical education and sports, aside from their benefits on motor abilities, provide enjoyment, companionship, and a sense of accomplishment, which are important for the development of confidence and self-image in all children and adolescents.[10] A periodic reinstitution of formal therapy may be necessary for defined reasons, such as to regain preoperative function after immobilization for orthopedic procedures or to learn new skills that have become appropriate and feasible for the child's developmental level and physical abilities.

Lower extremity orthoses or splints are used to improve function—for example, toe walking—or to prevent deformity in a child who does not ambulate.[5,17] Extensive bracing does not enable a child with severe motor disability to attain useful walking. Despite these considerations, the treatment team

might elect to use orthoses for passive standing or exercise ambulation in a bright, well-motivated youngster. The family, however, must understand clearly the limited purpose of these attempts.

Orthopedic surgery plays an important role in the treatment of physical disability.[5,21] Correcting abnormal posture and gait enhances the efficiency of walking. Nonambulatory children are more likely to need surgical procedures for preventive reasons, such as the release of spastic hip flexors, adductors, and femoral osteotomy for hip subluxation, which would otherwise progress to painful dislocation.

Selective posterior rhizotomy is a neurosurgical procedure suggested to decrease spasticity.[22] Phenol blocks of the motor points or motor nerve branches of selected muscles produce a reversible chemical neurolysis and temporary reduction of spastic hypertonia lasting four to six months.[23] Dantrolene sodium and diazepam are antispasticity drugs that are helpful in some patients.[23]

Associated Disabilities

Speech and language development need close monitoring because effective communication is one of the most valuable functional assets.[5,9] All children with cerebral palsy should have an audiologic examination and a timely correction of hearing impairments that may have detrimental effects on language acquisition. Sensorineural hearing loss is the characteristic auditory deficit and is particularly common in patients with kernicteric athetosis. Central language disorders are more likely related to cognitive dysfunction because young children show good recovery from aphasia after suffering damage to the dominant hemisphere. A subtle impairment of language competence may persist despite fluent speech, however, and also has been reported with congenital right hemiparesis.[9] Speech defects occur in athetosis and bilateral spastic paresis when pseudobulbar palsy affects the coordination of muscles that participate in phonation and articulation.[5,9] The resultant speech impairments range from mild articulation disorder to severe dysarthria with a total lack of functional verbal communication.

Therapy for speech and language deficits should commence as soon as the deficits are detected.[5] An important advance in the treatment of severe speech defects is nonverbal communication.[5,9,24] The simplest initial method is the simultaneous presentation of several objects or an improvised communication board of pictures from which a child can select the appropriate response by eye gaze, pointing, or any other consistent signal. When education and social interaction demand an expanded repertoire of communication skills, manually or electronically operated voice and printed word-symbol communicators offer various choices.[5,9,17,24] The potential for nonverbal communication should be explored when speech is delayed to identify children who have sufficient cognitive language ability to master this mode of interaction.

Feeding difficulties and salivation are additional signs of pseudobulbar palsy. Skillful feeding and carefully selected food textures facilitate oral motor function.[5,9,11,12] In almost all patients, dysphagia and drooling are reduced with time. In severe cases, inadequate nutritional intake or recurrent aspiration necessitates temporary or permanent feeding gastrostomy. For the socially embarrassing handicap of drooling, there are behavioral, pharmacologic, and surgical treatment methods.[5,9]

The possibility of a seizure disorder must be investigated in every patient.[5] Although seizures can occur in any clinical type of cerebral palsy, spastic hemiparesis and quadriparesis have the highest incidence rates. The selection of anticonvulsant medications depends on the clinical seizure manifestations, with consideration given to side effects on behavior and alertness.

A complete diagnostic assessment includes the evaluation of visual function.[5] Strabismus, most common in diplegia and quadriparesis, refractory errors, and retinopathy of prematurity require ophthalmologic treatment. Severe visual impairment or blindness has an adverse influence on motor development and ultimate level of physical function.

Patients with spastic quadriparesis, rigid or atonic clinical types, have the highest relative frequency of mental retardation and severe intellectual deficits.[5,9] In general, cognitive impairment is mild and occurs at a lower rate in those with hemiparesis and diplegia. Discrete lesions of the basal ganglia spare intellectual function in those with athetosis following kernicterus, but this may not be the case when hypoxic encephalopathy is a contributing factor.[5] Dysfunction of central perceptual processing may be a cause of learning disability despite satisfactory intellectual function.

Planning for appropriate educational placement begins before a child reaches school age and involves the cooperation of the family, educators, and the rehabilitation team.[5] Psychological assessment should be obtained before the child enters school. The psychologist must have experience with physical disabilities because the standard test batteries rely on motor items, verbal responses, and timed performance, which place children with impaired hand dexterity or speech at a disadvantage. In selecting suitable schooling, intellectual function is the deciding factor.[5,9] If necessary, adaptations in classroom environment should accommodate the physical disability. The Education for All Handicapped Children Act of 1975, PL 94-142, includes provisions for the least restrictive environment pertaining to educational goals. It must be stressed that education is a high priority for disabled children, whose future employment opportunities will be contingent on scholastic competence.

Psychosocial Issues

Initial counseling of the family revolves around diagnosis, outcome, and treatment.[5,9] Discussions about these issues and about special concerns of child rearing should be ongoing during the course of treatment. At the appropriate age, discussion and counseling should involve the child. Education and vocational preparation come into the foreground by school age. Concern with the physical disability should not distract attention from the emotional and social needs of childhood and adolescence. Disabled youngsters need the same variety of life experiences as all other children to develop emotional resilience, personal determination, and social skills.[5,9,10,18] These traits of behavior, though less tangible than the physical aspects of function, are essential for success in adulthood and originate from interaction between the child and family.[25]

Predicting Outcome

To predict the functional outcome and long-range achievement, the physician must weigh many diverse factors. Physical and intellectual abilities determine the highest possible function, but long-term studies show that the greatest

fulfillment of potential depends on psychosocial characteristics as well.[5,9,19,25]

Expectations in motor function, considering solely the physical disability, vary by the clinical type of cerebral palsy.[5,19] Children with hemiparesis walk between 1½ and 3 years of age. Although there are individual differences in assistive function of the affected hand, hemiparesis does not interfere with independence in usual daily activities. The outlook for ambulation is less uniform in children with bilateral lower extremity spasticity or dyskinesia. Independent sitting by the age of 2 years is a favorable sign for the eventual ability to walk, whereas an inability to sit at 4 years of age indicates a poor prognosis for ambulation.[5,19,20] Between 80% and 90% of children with diplegia, approximately half of those with quadriparesis, and three fourths of those with dyskinesia eventually are able to walk. The attainment of sitting by age 1½ to 2 years has a good correlation with community ambulation. The walking ability of children who learn to sit between the ages of 2 and 4 years probably will be limited to short distances outdoors or household ambulation with assistive devices or partial wheelchair use. The outlook for ambulation is generally good in children with ataxia. Independence in activities of daily living is expected of children with diplegia and those with quadriparesis who walk. Partial self-sufficiency in daily skills is a possibility for some children with quadriparesis who can use wheelchairs. Approximately 25% of children in this group require complete help. Dyskinetic and ataxic movement disorders may be more disabling in fine hand dexterity than in walking. The few patients with rigid or atonic clinical type have a poor overall functional prognosis. In general, mental retardation delays but does not exclude ambulation if the physical disability permits it. On the other hand, expectations in skills of daily life must be adjusted to a level commensurate with intellectual competence.

The estimated employment rate among persons with cerebral palsy, some in sheltered work, is approximately 50%.[5] One study compared vocational predictions at ages 7 to 16 with adult achievements.[25] Most young adults achieved or exceeded the predicted vocational status; only 28% did not. These results illustrate that vocational outcome depends on a complex interaction of many factors. Strong family support and personal determination were found to be characteristics common to those who did better than expected. Integrated education, vocational counseling, community-based independent living programs, and technologic advances were additional factors contributing to success according to this and other studies.[5,25]

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Rehabilitating Elderly Cardiac Patients

J. MICHAEL ANDERSON, MD, *Baltimore, Maryland*

The aging cardiovascular system undergoes many anatomic and physiologic changes. Increased vascular resistance, myocardial "stiffness," abnormalities of rhythmicity of the sinoatrial node, irregular cardiac rhythms, and alterations in heart rate and blood pressure responses are all seen more frequently in older patients. These changes are likely to impair these patients' ability to make the rapid adjustments necessary to maintain cardiac output during exercise and activity. When cardiovascular disease processes are superimposed on the "normal" concomitants of aging, greater alterations in hemodynamic response to exercise activity are noted than usually occur in younger cardiac patients.

Exercise testing of older cardiac patients is safe and is usually needed to prescribe an appropriate intensity of exercise activity. The choice of the exercise protocol, the timing of the exercise test in relation to taking prescribed cardiac medication, the choice of exercise equipment, and special considerations for devices such as pacemakers and automatic implantable cardiodefibrillators must be considered before the exercise test is done. Many of these factors and the presence of either silent or overt cardiac symptoms or untoward hemodynamic events will also affect the exercise prescription. Elderly patients usually show substantial functional improvement when participating in a cardiac rehabilitation program and comply well with prescribed exercise. Early educational intervention may be crucial to reducing disability in these patients.

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The process of cardiac rehabilitation in elderly patients (older than 70 years) must take into account the nature of the cardiac problem, concomitant illnesses, and the physiologic response to both exercise activity and the medical management of any underlying cardiac condition. Heart diseases occurring in the elderly include specific types of valvular disease and conduction disturbances that are associated with degeneration of the connective tissues of the heart.[1] Although the heart mass remains normal or decreases somewhat in size with aging, the endocardium diffusely thickens. The thickening is associated primarily with increases in fibrosis and the amount of collagen fibers, particularly in the left ventricle and atrium. The heart valves, particularly the mitral and aortic, become more fibrotic with age and both thicken and become more rigid. Usually these morphologic changes produce no notable hemodynamic changes. In more advanced cases, substantial aortic stenosis or aortic or mitral valve insufficiency can occur, predisposing to other cardiovascular problems including cerebrovascular accidents, left atrial enlargement, and secondary atrial fibrillation. Older "normal" persons usually have a number of additional relatively minor physiologic changes that are fairly widespread. The mean heart rate decreases with age. The inherent rhythmicity of the sinoatrial node changes, and irregular cardiac rhythms develop at an increased rate with both exercise and activity.[2,3] The maximum heart rate achievable during exercise also decreases with age (Table 1).[4] Peripheral vascular resistance in elderly patients is increased, primarily due to atherosclerosis and increased rigidity of the arterial system. The systolic blood pressure usually increases more than the diastolic pressure. These opposite heart rate and blood pressure responses to exercise offset each other so that cardiac work does not reflect an age-related change. A decline in cardiac output is noted, however, primarily because of a decreased stroke volume. The cardiac index may decrease by 0.8% per year with aging, with older subjects having greater difficulty increasing their cardiac output during maximal exertion.[5] The change in left ventricular ejection fraction from resting to exercise values decreases with age and appears to be lower in older persons. Higher filling pressures are noted in the "normal" older population in association with the higher cardiac output of exercise activity. This is primarily due to "stiffness of the myocardium" associated with the structural changes already described. In addition to the degenerative heart diseases occurring specifically in elderly persons, cardiovascular dysfunction will also arise from heart diseases that have continued from a younger age (Table 2).[1]

These normal and abnormal physiologic changes in the cardiovascular system with aging frequently impair elderly patients' ability to make the rapid adjustments necessary to maintain cardiac output at all times and under all conditions. Elderly patients are more vulnerable to the development of transitory episodes of heart failure and are predisposed to syncope and falls as a result of momentary and sudden discrepancies between cardiac output and that necessary to maintain adequate cerebral flow.

These cardiovascular and hemodynamic changes are superimposed on a general reduction in physiologic function by humans. The decline in functional capacity has been estimated at 0.75% per year after age 30.[6] A decline in muscle strength and mass and basal metabolic rate, generalized "dehydration" with decreased intracellular water content, an increased amount of body fat, a decrease in respiratory function, changes of the nervous system with a decrease in the cell

From the Sinai Rehabilitation Center, Baltimore, Maryland.
Reprint requests to J. Michael Anderson, MD, Sinai Rehabilitation Center, Belvedere at Greenspring, Baltimore, MD 21215-5271.

ABBREVIATIONS USED IN TEXT

AICD = automatic implantable cardiodefibrillator
ECG = electrocardiogram

number within the central nervous system, altered peripheral nerve function with slowing of the nerve conduction velocity, and alterations in the skeletal system including reduced bone density may all contribute to the declines in work capacity and capability of doing exercise activity.

Morphologic changes also develop in cartilage, ligaments, and tendons, which decrease flexibility with advancing age.[7] Muscles show an alteration in fiber type with the development of a more homogenous composition and a disproportionate loss of fast-twitch type II fibers that results in a 50% reduction in senile muscle mass compared with normal adult muscle.[8] Changes in oxidative metabolism also become manifest in old age. All of these factors result in a decreased capability to continue specific tasks. Both the underlying substrate of these "normal" changes and other adverse changes brought about by coexisting noncardiac disease processes must be considered when developing a physical exercise and activity program for elderly cardiac patients.

The prescription of aerobic exercise activity should be preceded and followed by appropriate warm-up and cool-down exercises, each varying from 5 to 15 minutes in duration. The interposed dynamic phase of exercise needs to be individually prescribed to fit the capabilities of each patient participating in a cardiac rehabilitation program.[9-13] A low-level exercise test or submaximal test is often used to monitor safety with exercise activity and to obtain an appropriate exercise prescription. Guidelines promulgated by the American College of Sports Medicine require that exercise testing be done in all older persons with or without symptoms and with or without known cardiac disease (Table 3).[4] The frequency and duration of exercise participation is similar to that prescribed for younger patients with cardiac disease and for healthy adults (Table 4).[14] Older cardiac patients have no increased risk when performing exercise activity and have an improved attendance ratio compared with younger patients.[12] Lower training intensities are used in older cardiac patients during the exercise sessions. This is because of the reduced functional capacity noted on exercise testing. Because maximal heart rates are easier to obtain on an exercise test than are peak oxygen uptake values, they are more often used in prescribing the intensity of exercise activity.

Exercise tests for prescribing an exercise program in older cardiac patients should not be done in the standard manner. Older patients participating in a cardiac rehabilitation program already have established cardiac diagnoses, and a physician doing exercise testing is not usually trying to determine whether myocardial ischemia exists as evidenced by the presence of signs or symptoms suggestive of cardiac disease. The physician's focus is primarily on generating safe indices for the exercise prescription. This focus mandates that every effort should be made to do the test under conditions that most closely simulate the exercise activity in which a patient will be participating. There is no need to discontinue cardiac medications, as is usually done for standard exercise testing to reduce the likelihood of having false-positive or -negative tests. The patients need to continue their cardiac medications. The exercise test should be scheduled in a time frame that coincides with the proposed time for exercise so that the effects of these medications on heart rate, blood pressure, electrical potential (electrocardiogram), and symptoms will be as closely simulated as possible. Adhering to these guidelines will result in the most accurate prescription possible and reduce the likelihood of the subsequent development of complications with exercise activity that could occur if the patient were tested during a time when a medication was at a peak or trough level. Untoward hemodynamic responses to exercise, such as the occurrence of angina or other cardiovascular symptoms, may also be avoided by following this procedure.

The type of exercise activity to be prescribed for a patient should be reflected in the selection of the exercise test protocol whenever possible. Patients often have higher heart rates using an upper extremity ergometer or stationary cycle than when walking or using a treadmill. Musculoskeletal or neurovascular deficits may be more functionally limiting to patients than their cardiovascular dysfunction with certain types of activity. It is therefore advised that, whenever possible, patients be tested on the type of equipment and with the exercises they will be using. Cardiac rehabilitation personnel working with elderly patients should become familiar with and use exercise test protocols comprising a variety of exercise equipment in addition to the standard treadmill tests.

Exercise testing in a patient older than 65 years is not associated with an increased rate of medical complications.[15,16] Exercise tests during the first three to six weeks after a myocardial infarction are best done using a submaximal test.[17] After this time subjective maximal exercise testing can usually be done safely. Typically the test will reveal a low aerobic work capacity of about 3 mets.* Maximal heart rates

*A met is a unit of measurement of heat production by the body—the metabolic heat produced by a resting-sitting subject, being 50 kg-cal per m^2 of body surface per hour.

TABLE 1.—*Maximum Heart Rate Predicted by Age and Conditioning**

Maximum Heart Rate, %	*Age, yr* 20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
Unconditioned															
100	197	195	193	191	189	187	184	182	180	178	176	174	172	170	168
90	177	175	173	172	170	168	166	164	162	160	158	157	155	153	151
75	148	146	144	143	142	140	138	137	135	134	132	131	129	128	126
60	118	117	115	114	113	112	110	109	108	107	106	104	103	102	101
Conditioned															
100	190	188	186	184	182	180	177	175	173	171	169	167	165	163	161
90	171	169	167	166	164	162	159	158	156	154	152	150	149	147	145
75	143	141	140	138	137	135	133	131	130	128	127	125	124	122	121
60	114	113	112	110	109	108	106	105	104	103	101	100	99	98	97

*From American College of Sports Medicine.4(p170)

TABLE 2.—*Heart Diseases in Old Age**

- Heart diseases from younger age
  - Congenital
  - Hypertensive
  - Ischemic
  - Rheumatic valvular disease
  - Syphilitic aortic regurgitation
  - Mitral regurgitation
    - Papillary muscle dysfunction
    - Ruptured chordae tendineae (due to endocarditis)
  - Cor pulmonale
  - Conduction disturbance (inflammatory, ischemic)
- Heart diseases specific for aged
  - Mitral regurgitation
    - Ring calcification
    - Ring dilatation
    - Ruptured chordae tendineae (due to degeneration)
    - Nodular sclerosis
  - Calcified aortic stenosis
  - Degenerative aortic regurgitation
  - Conduction disturbance (chronic)

*From Sugiura et al.[1(p535)]

are notably reduced below that predicted for age. Frequently there is also a reduced increase in the rate-pressure product comparing rest with maximal exercise values.

In addition to obtaining appropriate measurements for exercise prescription, the exercise test is also helpful in stratifying risk.[18] In particular, those patients older than 70 in whom ventricular arrhythmias develop during the exercise test have a substantial reduction in life expectancy as compared with the nonarrhythmia group.[19]

Most elderly patients with a cardiac disorder will be using one or more medications. Frequently these drugs will have an effect on the cardiovascular indices both at rest and with exercise activity. The reduction in heart rate, both at rest and during exercise, is related to the amount of β-blocking medication used. Although the heart rate is lower in persons using these medications, the maximal oxygen consumption and rate-perceived exertion do not appear significantly affected.[20] Therefore, the method used to calculate the exercise prescription using the heart rate response is not changed because the patient is taking a β-blocker.

The concurrent use of both heart rate response and rate-perceived exertion is helpful for monitoring exercise activity in elderly patients.[21] This is particularly the case when medication dosages or medications are changed. During the period of medication adjustment, patients can continue to exercise to their assigned rating of perceived exertion, rather than to the previously established target heart rate. Once the new dosage of medication has been equilibrated, the typical heart rate achieved at the prescribed rating of perceived exertion can usually serve as the "new" target heart rate. This method of adjusting target heart rates often precludes the necessity of repeating an exercise test. The target heart rate so determined can be corroborated at the next regularly scheduled exercise test done to establish the accuracy of the prescription and to monitor continued progress in improved functional capacity according to the protocols established by the cardiac rehabilitation program.

Some elderly patients will have limited exercise capabilities because angina occurs before they reach maximal functional capacity. For them, the target heart rate should be established at 5 to 10 beats per minute below the angina threshold.[22] Patients with angina will show substantial functional improvement because the angina threshold is raised as the result of a reduced heart rate-pressure product at each level of submaximal exercise.[23,24] The use of intermediate- or long-acting oral nitrates may also be helpful in elderly cardiac patients with angina. When taken before initiating exercise activity, the resulting vasodilatory effects on both the general vasculature and the coronary arteries may allow them to exercise at a higher level. Nitrates should be used with caution in the elderly, however, because of the associated risk of hypotension and syncope with an increased risk of falling. When adding oral nitrates to an exercise program, patients should be monitored more intensely with an increased frequency of blood pressure and pulse determinations and continuous electrocardiographic (ECG) monitoring. This ensures that no untoward hemodynamic or ECG problems occur at the higher level of exercises and that the medications are being well tolerated. Despite these concerns with the use of nitrates, the medications can be effective in elderly patients who have a low tolerance to exercise activity because of the early occurrence of angina. This strategy has allowed elderly cardiac patients to participate in an exercise program with a subsequent improvement in function that has translated into improved performance with their usual daily activities.

Older patients found to have silent myocardial ischemia with significant ST segment depression should similarly be provided with a target heart rate response of 5 to 10 beats lower than the "threshold level" at which ST segment depression was noted.

Some elderly patients with cardiomyopathy may also benefit from a cardiac rehabilitation program. These patients should be exercised at a substantially lower intensity, with the initial prescription being 60% to 65% of that safely achieved on a graded exercise test. Studies are not available comparing outcomes in these patients, but anecdotal reports and experience show that these patients do achieve benefit with increased functional capacity resulting from their participation in a cardiac rehabilitation program.

Elderly patients who have had pacemakers inserted also show notable improvement in work capacity after participat-

TABLE 3.—*Guidelines for Exercise Testing in Persons With Known Cardiovascular, Pulmonary, or Metabolic Disease**

	Patients' Age, yr					
	Apparently Healthy		Higher Risk			With Disease
			< 35	≥ 35		
Recommendation	< 45	≥ 45	No Symptoms	No Symptoms	Symptoms	Any Age
Maximal exercise test before an exercise program	No	Yes	No	Yes	Yes	Yes
Physician attend for maximal testing	No (< 35)	Yes	Yes	Yes	Yes	Yes
Physician attend for submaximal testing	No	No	No	Yes	Yes	Yes

*From American College of Sports Medicine.[4(p7)]

TABLE 4.—*Guidelines for Exercise Prescriptian far Healthy Adults and Cardiac Patients**

Population	Exercise Variables			
	Frequency	Intensity Level	Duratian, min	Mode
Healthy adult	3 to 5 ×/wk	60% to 80% $\dot{V}o_2$	15 to 60	Aerobic activities, weights, games
Cardiac patients				
Angina	3 to 5 ×/wk	70% to 85% anginal threshold	15 to 60	Walk, jog, bike
MI or CABG				
Phase I	2 to 3 ×/d	HR rest, 20/min	5 to 20	Range of motion, ambulation stairs
Phase II	3 to 4 ×/d	HR rest, 20/min, or 50% to 70% $\dot{V}o_2$	15 to 60 30 to 60	Range of motion, walk Range of motion, walk, bike, arm ergometry
Phase III	3 to 4 ×/wk	50% to 80% $\dot{V}o_2$	30 to 60	Range of motion, walk, jog, bike, swim, games, weights
PTCA	†	†	†	†
Transplants (outpatients)	3 to 4 ×/wk	RPE, 12 to 14/min	15 to 60	Range of motion, walk, bike, arm ergometry
Fixed-HR pacemaker	3 to 4 ×/wk	Systolic blood pressure, 60 to 80 mm of mercury	15 to 60	Walk, jog, bike, swim, games

CABG = coronary artery bypass graft (procedure), HR = heart rate, MI = myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty, RPE = rate-perceived exertion, $\dot{V}o_2$ = maximal oxygen consumption

*From Ward et al.14(p204)
†The same as for patients with Phase III MI or CABG.

ing in a cardiac rehabilitation program as compared with their functional capacity before the insertion of a pacemaker.[25] Recent advances in pacemaker construction allow for faster rate responses with exercise, with a smoother, more physiologic transition toward the upper rate limits of the devices.[26] Because of the improved surgical techniques and the advances in pacemaker technology, implanting pacemakers in the elderly has become relatively simple[27] and has resulted in less reluctance to do so. Patients with a ventricular demand pacemaker increased their cardiac output by increases in stroke volumes. Elderly patients who are paced at a constant rate cannot use a target heart rate for monitoring the response to exercise activity. The rating of perceived exertion and blood pressure measurements should be checked frequently to ensure the adequacy and safety of exercise activity and to prevent untoward hemodynamic events.

Elderly patients are now being referred for cardiac rehabilitation after having had an automatic implantable cardiodefibrillator (AICD) inserted. These patients can participate safely in cardiac rehabilitation programs and show improved functional capacity.[28] Target heart rates in patients who have had an AICD should not be established based on maximum heart rates achieved during a graded exercise test. The AICD has a preprogrammed heart rate cutoff point above which it will deliver a shock if it senses a wide QRS tachyarrhythmia. For this reason, it is important to assess the heart rate cutoff of the AICD and to use this information in prescribing a target heart rate. This cutoff heart rate should not be approached during exercise activity, particularly in the case of patients with ventricular conduction defects. In selected patients who have AICDs, the use of β-blockers may help limit the heart rate response during exercise to prevent the AICD from discharging. Monitoring of these patients during cardiac exercise is otherwise unchanged.

The use of telemetry ECG monitoring in the elderly cardiac population varies widely. Most cardiac rehabilitation programs use ECG monitoring only during the first two or three weeks of program participation after a myocardial infarction or cardiac operation.[29] Continuous ECG monitoring is otherwise reserved for "high-risk patients," including those patients having severely depressed left ventricular function, complex ventricular arrhythmias at rest, ventricular arrhythmias appearing or increasing with exercise, falls in systolic blood pressure with exercise, a history of sudden cardiac arrest, and coronary artery disease or pronounced exercise-induced ischemia. Unfortunately, there are no controlled studies comparing the safety of exercise in elderly patients who have undergone training with on-site medical supervision with and without continuous ECG monitoring. Some patients have difficulty self-monitoring their heart rate response during exercise activity. Many of these have been able to master the rate-perceived exertion rating. As the perceived exertion rating correlates well with both heart rate response and oxygen consumption, these patients can often do without continuous ECG telemetry.

Patients should record their resting heart rate and perceived exertion rating and have their blood pressure checked on entry to the exercise area, at the end of warm-up exercises, every 5 to 10 minutes during active participation in the exercise activity, and at the end of their cool-down exercises. Electrocardiograms should be taken whenever a patient experiences a change in regularity of heart rate or if any untoward cardiac signs or symptoms are noted. Baseline ECGs should also be taken at the start of the program and at monthly intervals thereafter. Elderly patients who have had recent changes in cardiac medication or dosages may also need continuous ECG monitoring until they have shown appropriate stability on their new medication regimen.

Poor compliance of elderly patients in participating in exercise activity was strongly correlated with a lack of adequate information.[30] Other factors associated with reduced compliance in the elderly included a lack of motivation, an extremely lowered exercise tolerance, socioeconomic problems, and associated diseases. Patient education offered concurrently with the exercise program appeared to have a synergistic effect with attendance at both educational and exercise portions of the program. For example, smoking cessation after myocardial infarction was significantly higher among patients participating concomitantly in an exercise training group as compared with a nontraining group of patients.[31] Patients who have psychological impairment and disability within three months after a myocardial problem have shown increased problems with passive hopelessness and resignation to a life of dependency and incapacity with as long as three years' follow-up.[32] Early intervention with education and support may be crucial to reducing disability among these elderly cardiac patients. Social and emotional function also substantially improves in patients participating in the

educational portion of a cardiac rehabilitation program.[33] Older adults desire and are able to learn new activities. Educating elderly cardiac patients is worth the time and effort involved. Associated health problems and age-related deficits that adversely affect learning in these patients should be viewed as handicaps that can be overcome. Dietary instructions for weight loss, control of hyperlipidemia, control of sodium intake, and modifications for other specific diseases are important educational topics. Smoking cessation and stress management are other topics that should be covered in the educational portion of a cardiac rehabilitation program.[34]

Medicare currently reimburses cardiac rehabilitation, hence reimbursement is often less of a problem for older patients than for persons younger than 65. Medicare contracts with intermediaries vary state by state and regionally. Because of this, implementation of Medicare guidelines may vary from state to state, depending on the administrative policies established by the various intermediaries. Patients must have a "clear medical need" and be referred by a physician. Determining the medical need usually consists of documenting within the preceding 12 months a diagnosis of acute myocardial infarction, a coronary artery bypass procedure, or having stable angina pectoris.[35] Reimbursement is subject to program restrictions and limitations. In some areas these include such criteria as requiring that a physician be on the premises and available to administer medical care at all times that the facility is opened; having immediately available cardiopulmonary emergency diagnostic and life-saving equipment; conducting the cardiac rehabilitation program in an area of the facility that has been set aside for the exclusive use of the program while in session; having the cardiac rehabilitation programs staffed by personnel who are trained in both basic and advanced life support techniques; and having personnel who are specifically trained for exercise therapy for coronary artery disease.

Within the next decades, substantial changes are likely to occur in the provision of cardiac rehabilitation to older and younger patients. The typical 12-week program, developed primarily because Medicare and other guarantors have reimbursed courses in 12-week blocks of time, will likely be done away with. The stratification of patients according to risk has been stressed in several publications.[36-39] Low-risk cardiac patients may be allowed to participate in programs for only as short a time as two to three weeks before being weaned to a "maintenance" program. Intermediate-risk patients will probably be approved for programs of six to eight weeks' duration with an increased intensity of monitoring. High-risk cardiac patients may be approved for 12 to 36 or more weeks of participation, with much more intense monitoring, possibly including continuous ECG monitoring by telemetry. Reports from the American College of Physicians and the American College of Cardiology that recommend similar guidelines appear to have been accepted in principle by guarantors and are the basis of the current policy guidelines for some Blue Cross and Blue Shield districts.[40] The effect of these programmatic changes on elderly cardiac patients may be much greater than on younger cardiac patients, particularly as the educational components will be most adversely affected. The elderly, many of whom show a decreased rate of new learning and have increased difficulty mastering self-monitoring techniques and assimilating information from educational programs, will be at a distinct disadvantage. These difficulties, coupled with a lack of reimbursement for the educational component of cardiac rehabilitation programs, will intensify the difficulties associated with providing appropriate patient education to augment the benefits of the exercise activity portion of cardiac rehabilitation in elderly patients. Hence, providing an appropriate educational component for elderly cardiac patients and their families may be the greatest challenge physicians working with these patients face in the 1990s.

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MY LUCKY STROKE

It was snowing hard when I turned the corner
off the highway into Bear Canyon Road . . .
lit a fire in the old wood stove
made four trips
up and down the inside twisting stairs
to bring wood enough for a day and night . . .
made lunch

I felt my right foot dragging now and then
my right hand slow to move . . .
odd sensation in the middle of my head
like a loose connection
and a bulb blinking once in a while
I figured sleep would fix it
but in the morning, worse, much worse
I called my wife and grandson
to come and get me
and over the phone I sobbed
having to ask for help
my wife knew at once
what the trouble was
we're going to the hospital

"You'll have to stay over"
surprised me I felt good
but they have to do tests
and you've a slur in your speech . . .
wheeled me out and left me in the hall
for over an hour no bottle to pee in
unable to move . . . what they said
stay in the hospital to avoid any trauma
they never heard of humiliation . . .
on Thursday the young nurse
said here's the stuff wash yourself
my right hand couldn't reach my left armpit
I practiced that all day
and next day I could reach it
Dot left me her tiny squeeze flashlight
to practice gaining grip . . .
cards flowers friends
in four days I talked so much
most of my slur disappeared
my wife Dot brought me clothes and courage . . .

I could see in the mirror
my slack right cheek
and my eye unable to wink
I practiced almost every hour
raising my cheek muscles
and winking my eye at fate
and my lucky stroke at seventy-five
it was the winking taught me
no more alcohol or cigarettes
I couldn't straighten out
the first two fingers of my right hand
so I held them closed with my left
and made them work to straighten out . . .

II
Casa Colina, in the stroke unit

Dot kissed me goodbye
in a room with four we're caught in a common net
feel the bond and help each other get out . . .
group session discussions . . .
testing memory and meandering . . .
lunch and dinner in the dining room
get yourself there in your old wheelchair
no footrests for the weak leg learn to paddle walk
use your arms to turn the wheels
leg gets tired arm gets tired
you want to eat get your ass in there
that's me talking to myself

Dot came for dinner almost every day
brought bookkeeping from the store
a great big help to me
to know that I was needed . . .
a lot more could be done
to help the patients help themselves
be innovative with their wheelchairs . . .
sometimes I went begging
for someone to walk with me
I couldn't have a walker or walk alone
when therapists and aides were busy
Andrea would get away from head injury
and help or nephew Fred from publicity
would spare a few minutes

I wish I could remember her name
that aide was not pretty but vital
firm in friendship single mother of two
I have a dozen hugs saved up for her . . .
finally out of my wheelchair walking free
how to get in and out of the shower
how to make coffee fill out a form
what do you want to do when you get home
I want to walk to work and to write . . .
one comment I hear
you're completely recovered
no one ever completely recovers
but learns new ways and quite likely for the better
I had thought I could do anything and as much
as I wanted
it took a lucky stroke to tell me
it just ain't so.

CHARLES CHASE©
Claremont, California

Charles Chase is pictured on the cover of this special issue busily working at one of his hobbies after recovering from the illness he describes in this condensation of his poem, "My Lucky Stroke." He owns a folk music store in southern California.

Effect of Exercise on Muscle Function Decline With Aging

JEROME W. GERSTEN, MD, *Denver, Colorado*

As people age, changes in muscle occur that are associated with a decrease in strength and endurance. These changes result in decreased functional capacity and quality of life. A substantial portion of this decrease is the result not of aging but of the sedentary life-style so frequently associated with aging. In "healthy old" persons and in older animals in experiments, an appropriate exercise program can result in increased strength and endurance. This is true both in longitudinal and short-term studies. As physical impairment increases, the exercise program must be individualized, and results are not as readily predictable. Much work remains before we may be certain how much exercise can be tolerated in these more impaired persons and what the effects may be.

(Gersten JW: Effect of exercise on muscle function decline with aging, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:579-582)

Life expectancy at birth has been steadily increasing from 25 years 2,000 years ago to 49 years in 1900 and to about 75 years now. Longevity trends suggest a finite limit to the human life span of about 85 years.[1] In addition to life-expectancy changes, changes have occurred in work patterns. The percentage of our population older than 65 years that continues to work is shrinking. In 1900, 75% of people older than 65 continued to work; this fell to 45% in 1950 and to only 10% in 1970.

The time period from retirement from employment, responsibilities, and economic activities to serious functional impairment can now reach 10 to 20 years. There has been a progressive increase in the period of possible serious functional impairment. The natural life span cannot be our only consideration. More important is our active life expectancy.[2] The ability to be independent largely determines the quality of our lives. Therefore, although many systems are important in determining functional status, the cardiovascular and neuromusculoskeletal systems play key roles.

Millennia ago, the combination of a relatively short life span and compassionate and protective attitudes toward the older population made a passive role by older persons acceptable. With the increase in the number and age of older nonworking persons, the rapidity of technologic change, and the weakening of kinship ties, older persons are now responsible for maintaining their independence.

The role of exercise in the life-style of young adults has been recognized by Western civilization for more than 2,500 years. The possible benefits of exercise in prolonging the independence of older persons have only recently been more widely addressed. Almost all organ systems show anatomic and physiologic changes with aging—changes that may be the specific result of aging but which also may represent illness or inactivity associated with aging. In this short discussion I will address primarily the cardiovascular and neuromuscular systems, note changes with aging, and examine the effects of exercise on these two systems in older animals or humans. The important issues of exercise and cardiac rehabilitation as well as exercise and osteoporosis will not be addressed.

Changes With Aging

Manifestations of aging appear in all systems and tissues. Biopsy studies of muscle in persons between ages 60 and 90 and older show evidence of both neuropathic and myopathic changes.[3] Frequent findings include group atrophy and type II atrophy, with a decrease in type II fiber diameter from 49 to 22 microns. Electron-microscopic study may show disorganization of sarcomere structure, aggregation and deformity of muscle nuclei, an increased number of mitochondria, abnormalities of satellite cells, moderate thickening of capillary basement membrane, and a decrease in and thickening of subsynaptic folds of the motor end plates. Aniansson and coworkers, in a single biopsy specimen of the right vastus lateralis, found fewer anatomic changes.[4]

In older persons the percentage of body fat increases; muscle mass, normally 46%, may decrease to 35%[5]; and urinary creatinine levels may fall. Muscle force decreases significantly,[6] and grip strength decreases.[7] After age 74, 28% of men and 66% of women may not be able to lift objects weighing more than 4.5 kg.[8] Although the diaphragm shows fewer morphologic changes than other striated muscle, inspiratory and expiratory pressures do decrease with age, the decrease being greater for the former.[9]

In aging rats, the weight of soleus and plantar muscles is decreased, rates of contraction and relaxation are slowed, and maximal twitch and tetanus tension are decreased.

With aging there is a decrease in the functional capacity of the cardiovascular system, with a decrease in the maximal oxygen uptake capacity ($\dot{V}O_{2max}$).[5,10] This decrease proceeds at a rate of about 10% per decade and may be due to a decrease in maximal heart rate and stroke volume or a decrease in oxygen extraction by the contracting muscle, with a lower maximal arteriovenous oxygen difference. Needle biopsy of the vastus lateralis shows a decrease of resting muscle oxidative capacity of 41% in older persons.[5] In older per-

From the Department of Rehabilitation Medicine, University of Colorado Health Sciences Center, Denver.

Reprint requests to Jerome W. Gersten, MD, Department of Rehabilitation Medicine, University of Colorado Health Sciences Center, Campus Box C243, 4200 East Ninth Ave, Denver, CO 80262.

ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
$\dot{V}_E$ = expired volume per unit of time
$\dot{V}O_2$ = oxygen consumption per unit of time
$\dot{V}O_{2max}$ = maximal oxygen consumption

sons, maximal ventilation ($\dot{V}_E$) decreases, the ventilatory equivalent ($\dot{V}_E/\dot{V}O_2$) increases substantially,[11] and there is a decrease in the expiratory flow rate, the forced expiratory volume in one second, and maximal voluntary ventilation.[12] In rats, myocardial mechanical performance decreases with age with a slowing in the velocity of muscle shortening, associated with a shift in the myosin isozyme form from the V_1 to the V_3 isozyme and a decline in the calcium-activated actomyosin adenosine triphosphatase (ATPase) activity.

Muscle strength and endurance, two aspects of muscle function, play important roles in the functional capacity of older persons. We will consider only these issues. Strength represents the maximal force or tension that can be developed by a muscle, measured in terms of pounds, kilograms, grams, or dynes. When a rotatory force (torque) is measured, the units may be foot-pounds or kilogram-meters. Strength may be measured with maximal isometric contractions (using strain gauge or isokinetic techniques at zero velocity) or approximated by noting the maximal weight that can be lifted in a single contraction. The five- or ten-repetition maximum introduces elements of work capacity and is less precise. The most reliable predictor of force development in muscle, though not the only one, is the cross-sectional area of the contracting unit, whether it be actomyosin threads, isolated glycerinated muscle fibers, isolated muscle in animal studies, or human kineplasty. The force developed is of the order of 30 to 40 grams per mm^2.

Exercise designed to increase strength emphasizes high force development (high-resistance exercise), relatively short durations of exercise (30 or fewer contractions at a rate of 10 per minute), and, if possible, repetition of this cycle a few times a day. In general, fatigue is not part of this process. Increased strength can usually be demonstrated early, with a plateau reached within four to eight weeks. During the early phase of this increase in strength, changes are presumed to be due to neurogenic factors, although it is possible that there may be shifts in extracellular fluid that mask changes in cross-sectional areas of muscle. Somewhat later, increases in cross-sectional muscle areas can be detected by computed tomography or circumferential measurements.

Endurance is measured by the work capacity of a single muscle or of the whole body when many muscles are active. This is measured as work performed—force times distance (foot-pounds, kilogram-meters)—or maximal aerobic capacity ($\dot{V}O_{2max}$: liters O_2 per minute, ml O_2 per kilogram per minute). With regard to a single muscle, the time it takes for force exerted to be decreased to 50% of the initial force, or the time that is required for muscle contraction to cease completely, could be measured. Maximal aerobic capacity may be measured with the subject on a treadmill, progressively increasing the velocity and grade until oxygen consumption per unit of time plateaus. Unlike strength, which depends primarily on the cross-sectional area of muscle and neurogenic factors, endurance depends on the ability to transport oxygen to active muscles (cardiovascular factors) and the ability of muscle to use the oxygen supplied (intrinsic muscular biochemical factors). Unlike training to increase strength, exercise to increase endurance requires sessions that are relatively long (30 to 40 minutes), repeated at least three times a week, and intense enough to raise oxygen consumption or heart rate to 60% or more of the maximum.

In general, improvement in a specific test is greatest when training provides an experience similar to that which is tested. This concept of specificity is not rigid, for it has also been shown that training in strength, for example, may also produce an improvement in endurance, though to a lesser degree.[13]

Effects of Exercise

In experiments in animals, controlled daily exercise may be associated with an increase in mean life span. A long-term exercise program in rats, beginning at three months, results in increased cardiac performance, total oxygen consumption, and oxidative capacity of skeletal muscle but does not change actomyosin ATPase activity or shift cardiac V_1 myosin isozyme composition significantly. The shift from V_1 to V_3 isozymes, characteristic of aging, is not altered.

Short-term studies in animals also have shown that older animals can respond favorably to exercise programs. Exercise can increase the plasma concentration of high-density lipoprotein cholesterol. In old rats trained at a level of 75% maximal capacity five times a week for ten weeks, the plasma triglyceride levels were lower than in old untrained rats and the acetyl-CoA carboxylase level (rate limiting in fatty acid synthesis) was higher than in old and young untrained rats but lower than in young trained rats.

The contraction time of slow- and fast-twitch muscle increases with age. In older rats, strength training increases soleus and plantar weight and swim training increases the heart weight. Strength training increases the rate of contraction and relaxation and the maximal twitch and tetanus tension in the soleus muscle. Strength training also increases the maximal twitch and tetanus tension in the plantar muscle.[14] There is a selective decrease in type II fibers with aging and a selective decrease in slow- and fast-twitch fibers in the soleus. Swim exercises, unlike strength exercises, increase aerobic capacity with increases in citrate synthase in the soleus and plantar muscles. Both strength and swim exercises increase hexokinase. Strength training, but not swimming, increases creatine phosphate and adenosine triphosphate levels.[15]

Rats were trained in a swimming program up to one hour a day five days a week for three months. In programs beginning at 1, 6, or 12 months of age, there was an increase in actomyosin ATPase levels. In programs begun at 6 months of age, there was an increase in creatine kinase levels. In programs begun at 17 to 22 months, there was a decrease in ATPase levels and a considerable decrease in creatine kinase concentrations, suggesting that there was a threshold age for strenuous exercise in rats.[16]

Improved mental health, feelings of relaxation, and decreased tension have been reported frequently as consequences of exercise. A lower incidence of cardiovascular disease after a regular program of physical activity has been noted,[17] and a higher incidence of fatal myocardial infarction has been reported in workers with low levels of physical activity. In a large study of Harvard alumni, an active lifestyle was associated with an increased life expectancy.[18]

In 37 men evaluated 31 years after the initial study, there was a decrease in $\dot{V}O_{2max}$ levels, an increase in $\dot{V}E/\dot{V}O_2$ with maximal work, a gradual decrease in the oxygen pulse (ml O_2 per beat), and a decrease in the maximal heart rate. There was a major difference in one subgroup during the last nine-year examination. This group, which increased its participation in sports—including squash, tennis, and skiing—showed an increase in $\dot{V}O_{2max}$ levels, an almost steady $\dot{V}E/\dot{V}O_2$, and an increase in oxygen pulse, manifesting an improvement in fitness and work capacity because of the change in exercise habits.[11] Champion middle-distance runners and nonathletes showed declines in $\dot{V}O_{2max}$ values and an increase in the $\dot{V}E/\dot{V}O_2$ after 30 years. In the middle-distance runners, the decrease in $\dot{V}O_{2max}$ was considerably less, the increase in $\dot{V}E/\dot{V}O_2$ was significantly smaller, and the blood lactate levels and heart rate were lower on walking.[19] Lung volumes and pulmonary function values may be 10% to 15% higher and the $\dot{V}O_{2max}$ 35% higher in older former athletes than in sedentary older persons.

Regular vigorous endurance exercise slows the $\dot{V}O_{2max}$ decline to about 5% per decade. Over an eight-year period, the $\dot{V}O_{2max}$ in former master athletes who continued physical activity decreased approximately 4.1%, but in sedentary controls the decrease was 9.7%.[10] The decrease in the $\dot{V}O_{2max}$ was presumably due to a decrease in the stroke volume or a decrease in oxygen extraction by muscle, or both. In an older group trained at an exercise level of 70% of $\dot{V}O_{2max}$ for an hour, the $\dot{V}O_2$ (milliliters per kilogram per minute) was greater than in older sedentary subjects, almost the same as in young sedentary subjects, but 24% less than in young trained subjects. The same pattern existed with respect to the $\dot{V}E$. Both trained groups had a greater increase in blood glycerol concentrations and showed an increase in the rate of lipolysis. The physiologic responses of the older trained persons were similar to those of the younger trained ones. Older healthy men could participate in an endurance type training program that was appropriate in intensity and duration for their age.[20]

Effects of Exercise—Short Term, Human

Generally favorable results following exercise have also been reported in "healthy older persons." Persons older than 60 exercising 30 minutes three times a week for 16 weeks at 70% of their $\dot{V}O_{2max}$ had a significant increase in maximal oxygen uptake. After a 4-month period, those who took their stationary bicycles home for continued exercise maintained this increase at 12 months. Those who were encouraged to exercise but did not take bicycles home did not show the increase in maximal oxygen uptake at one year. In addition to the change in $\dot{V}O_{2max}$, in those who exercised a new cardiac condition occurred in only 2.4%, but in a nonexercising group such a new condition occurred in 12.9%.[17]

In older subjects with an average age of 65 years, exercising for 45 minutes at 75% of heart rate reserve three times a week for 12 weeks resulted in an increase in muscle glycogen (needle biopsy of the vastus lateralis), though the levels were still lower than in younger subjects. The oxidative capacity of muscle, $\dot{V}O_{2max}$, and maximal ventilation were all substantially lower at baseline in the older subjects, but all increased considerably with the training program. There was evidence of peripheral adaptation.[17] Subjects aged 70 to 79 who exercised for 35 to 45 minutes three times a week for 26 weeks at levels beginning at 50% of $\dot{V}O_{2max}$ and reaching 75% to 85% of maximal heart rate were compared with others who exercised for about 30 minutes three times a week on a Nautilus apparatus.[6] The $\dot{V}O_{2max}$ values increased 22% in the endurance group and 4% in the strength-building group. The oxygen pulse increased 17% in the endurance group but did not change in the strength-building group. Lower body strength increased 5% in the endurance group and 9% in the strength group. Upper body strength decreased 6% in the endurance group and increased 18% in the strength group.

Women aged 63 to 88 (mean of 71) exercised three times a week for 25 weeks. A period of 10 minutes was devoted to aerobic exercise at 65% of maximal heart rate and 25 to 30 minutes in strength and flexibility exercise. Some women had small weights attached to their wrists and ankles, and others had no weights. A third group did not exercise. The two exercising groups had a significant increase in strength of shoulder internal and external rotators, elbow extensors (17%), and knee flexors (11%) compared with controls.[21] Range of motion increased significantly in shoulder flexion and abduction, in ankle plantar flexion, and in cervical rotation.

In sedentary men aged 60 to 72, training on a thigh-knee dynamic machine at 80% of one repetitive motion three times a week for 12 weeks produced an increase in dynamic strength (1 RM) of more than 100% in knee extensors and more than 200% in knee flexors. Static strength, with the knee flexed to 30 degrees, increased approximately 10% to 15%, and strength increase at 60 degrees per second was only about 10%. The increase in area, measured by computed tomography, was approximately 10% after six weeks. The area of type I fibers increased 33.5% and of type II fibers 27.6%. The distribution of fiber type did not change. Presumably there was a neural adaptation to specific training.[8]

Subjects aged 65 to 75 trained in a program stressing maximal sustained ventilatory capacity for eight weeks at least four days a week, with two 15-minute sessions a day, had an increase in ventilatory muscle endurance of approximately 20% and in maximal voluntary ventilation of 17%. The forced expiratory volume in one second did not change. Two months later, the improvement in ventilatory function was retained.[12]

There are fewer controlled studies on "nonhealthy older persons" who either have significant chronic disease or reside in nursing homes. Nursing home subjects, excluding those with serious cardiac disease or cognitive dysfunction, were trained at 80% of maximal heart rate three times a week for a year. The goal was to have a 15-minute program every day, but only 5 to 10 minutes per day was possible. There was little effect on overall endurance and possibly some small training effect in the arms. Problems with lower extremity disorders and intercurrent illnesses frequently intruded.[22]

A total of 49 chronically ill patients older than 64 exercised for 90 minutes three times a week for four months. They spent 10 to 15 minutes on stationary bicycles at 65% of maximal heart rate reserve and 20 minutes on strength and stretch exercises for low back and abdominal muscles. Of the 49 patients, 15 (31%) had 30 minutes of aerobic exercise in water once or twice a week. There were no controls. Cardiovascular function improved, as measured by increased met* levels, an increase in treadmill times, a decrease in resting

*A "met" is the metabolic heat produced by a resting-sitting subject, being 50 kg calories per m^2 of body surface per hour (*Dorland's Medical Dictionary*, 27th edition, WB Saunders Company, Philadelphia, Pa, 1988).

heart rates, and a decrease in submaximal exercise heart rates. Abdominal strength improved. Of the 49 patients, 13 (26%) dropped out of the study.[23]

In a group of 35 ambulatory patients aged 64 to 85 years, 28 (80%) of whom had degenerative joint disease, 11 (31%) hypertension, and 9 (26%) back syndrome, 18 were placed in an exercise group and 17 in a control group. Exercises were performed for an hour three times a week for 16 weeks and included endurance (with the target heart rate to 50% of the heart rate reserve), range of motion, coordination, and neuromuscular strengthening (chair strengthening exercises carried out for 20 minutes). There were no adverse reactions but no significant differences between the two groups in maximal metabolic work or neuromotor tests.[24]

It has been demonstrated repeatedly that anatomic and physiologic deterioration takes place in muscle tissue with aging, with a functional decline in cardiovascular and neuromuscular systems. It is now apparent, however, that much of this decrease in functional capacity is due not to the intrinsic processes of aging but to the inactivity and sedentary lifestyle of older persons.

In healthy older persons, especially the "young old" (65 to 75 years), exercise programs similar to those used in young athletes can substantially and meaningfully improve strength and endurance. With a further increase in age and progression of chronic illnesses, such routines of exercise can no longer be practiced. Shephard describes well the precautions and the individualized programs required in more functionally incapacitated older persons.[25] We still need more quantitative information with regard to the degree of improvement that might be anticipated in this more impaired population.

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REHABILITATION MEDICINE Adding Life to Years

Bilateral Lower Limb Amputee Rehabilitation
A Retrospective Review

MARGARITA M. TORRES, MD *and* ALBERTO ESQUENAZI, MD, *Philadelphia, Pennsylvania*

We retrospectively reviewed 61 cases of bilateral lower limb amputations in patients admitted to a regional amputee rehabilitation program. Of the 61 cases, 41 were analyzed as to functional outcome on discharge, at 1 month, and at 3 months; 20 were not included owing to transfers to acute care or loss to follow-up. There were 41 men and 20 women, the average age was 61.5 years, and 47 patients (77%) were discharged to home. There were 25 bilateral below-knee, 14 above-knee and below-knee, 12 bilateral above-knee, 5 below-knee and partial-foot, 3 above-knee and partial-foot, and 2 bilateral partial-foot amputations. The average length of stay for all levels was 24.2 days. Most of the patients at the time of discharge achieved a level of limited household walking with the exception of those with bilateral above-knee amputations. A significant improvement in function was noted for all patients at 3-month follow-up, with most patients achieving household ambulation level, but 10 remained independent at wheelchair level for mobility.

(Torres MM, Esquenazi A: Bilateral lower limb amputee rehabilitation—A retrospective review, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:583-586)

The appraisal of functional status is routine in medical rehabilitation, including ambulation status after inpatient rehabilitation programs.[1-13] A review of the recent literature, however, failed to show reports of functional outcomes for bilateral lower limb amputation.

In 1984 a seven-year retrospective review of the population admitted to a major metropolitan rehabilitation center described the characteristics of patients with lower limb amputation.[14] The review, when compared with national surveys done one and two decades previously,[15,16] indicated an increase in mean age, an increase in the number of below-the-knee over other amputation levels, and an increasing number of amputees readmitted for bilateral prosthetic training.

Sakuma and co-workers reported in 1974 their study of 53 elderly patients who had undergone bilateral lower extremity amputations.[17] They found that 50% of amputees with preservation of at least one knee joint could become ambulatory with prostheses for self-care purposes. They also concluded that a rehabilitation program was beneficial for both users and nonusers of prostheses.

Also in 1974, Kerstein and associates reported their study of 194 major amputations over a ten-year period.[18] Of the total group, 23% had bilateral amputations. At the conclusion of a 22-week postamputation rehabilitation program, 80% of the patients were able to return home and 70% of all patients were able to walk with just the use of a single cane or without aids.

The purpose of this study was to document patients' functional results after bilateral lower limb amputation on discharge from an inpatient rehabilitation program and at one month and three months after discharge. As the number of patients with bilateral lower limb amputations increases, there is a greater need to examine closely the efficacy of rehabilitation programs that have ambulation training as a goal.[14]

Patients and Methods

All patients with bilateral lower limb amputations who presented to a regional amputee rehabilitation center over an 18-month period (from July 1988 through December 1989) were selected. The outpatient records were reviewed retrospectively for the following information: patient demographics, including age and sex, amputation levels, length of inpatient rehabilitation stay, and disposition on discharge; and functional mobility on discharge, at one month, and at three months after discharge.

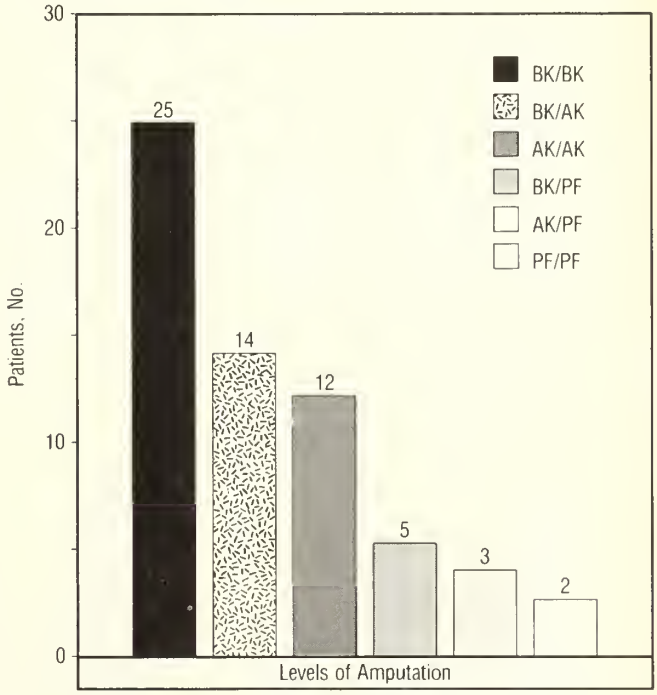

Figure 1.—The frequency of levels of lower extremity amputations is shown. AK = above the knee, BK = below the knee, PF = partial foot

From the Moss Rehabilitation Hospital and the Temple University Hospital, Temple University School of Medicine, Philadelphia, Pennsylvania.
Reprint requests to Margarita M. Torres, MD, Moss Rehabilitation Hospital, 1200 W Tabor Rd, Philadelphia, PA 19141-3099

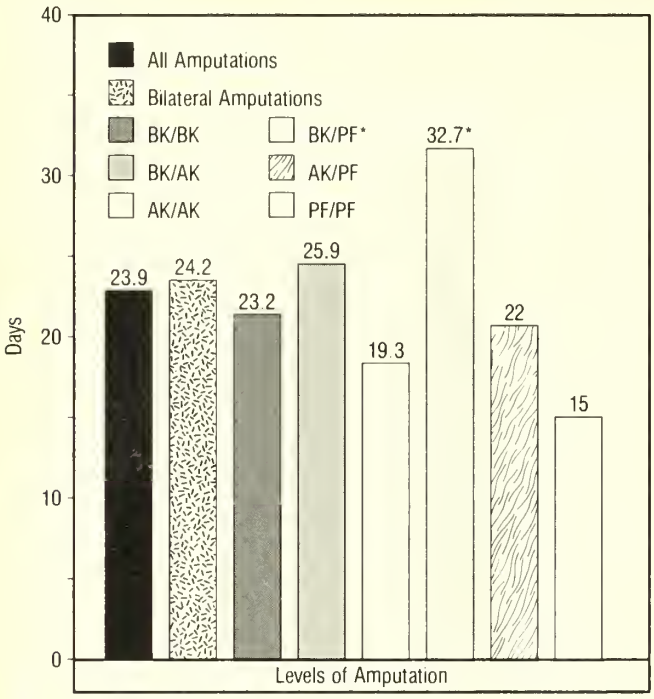

Figure 2.—The graph shows the average length of stay in days for inpatient rehabilitation for all lower extremity amputations, bilateral lower extremity amputations, and per level of amputations. AK = above the knee, BK = below the knee, PF = partial foot, * = corrected after 1 case omitted

The levels of amputation were defined as partial-foot, to include toe, Syme's, and transmetatarsal amputations; below-knee; and above-knee amputations. During the 18-month period, none of these patients had hemipelvectomy or hip disarticulation as their secondary amputation site.

Patients' functional status was examined on discharge and at one and three months after discharge in 41 cases; 20 were not included in this portion of the analysis because of transfers to acute care hospitals or loss to outpatient follow-up.

Patients' functional status falls into the following five groups:

- A limited household ambulator is a person who can use a prosthesis only in the home to ambulate independently and perform self-care activities. The distance for a limited household ambulator is less than 37 m (120 ft).
- A household ambulator can walk more than 37 m and performs all of the activities of daily living using prostheses.
- A limited community ambulator is a patient who can walk 152 m (500 ft), can participate in some avocational activity, but is not gainfully employed.
- A community level ambulator is one who can walk more than 152 m, engages in vocational and avocational activities, including driving with the prosthetic devices, and is gainfully employed.
- Although the wheelchair is used by all of them to attain greater mobility within the home or community, a person who uses a wheelchair exclusively for all mobility and activities of daily living is defined for the purposes of this study as a wheelchair user.

Results

Over an 18-month period, 2,941 patients were admitted to a major metropolitan rehabilitation center. Of these, 314, or 11%, were admitted to the regional amputee rehabilitation program and 61, or 19.4%, had bilateral lower limb amputations. As illustrated in Figure 1, the most frequent level of amputation was below both knees (25 patients or 41%), followed by below and above the knees (14, or 23%), and above both knees (12, or 20%), with less frequency of bilateral partial-foot, partial-foot and below-knee, and partial-foot and above-knee amputations.

Of the 61 patients, 41, or 67%, were men. Ages ranged from 29 to 88 years, with the average age being 61.5 years.

Figure 2 shows the average length of stay on the inpatient rehabilitation program, which for all amputations was 23.9 days and for bilateral amputations was 24.2 days, with the range being 3 to 78 days. The average length of stay for below-knee and partial-foot amputations was 37.8 days, although one patient's hospital stay was prolonged because of disposition problems, and the patient was eventually placed in a nursing home. The corrected average length of stay for this level of amputation was then 32.7 days.

Of the 61 patients, 47, or 77%, were discharged to home, 12 (20%) required transfer to acute care hospitals for medical or surgical complications, and only 2 patients were transferred to a nursing home for long-term care.

Of the 47 patients discharged to home, 17, or 36%, achieved a limited household level of ambulation at the time

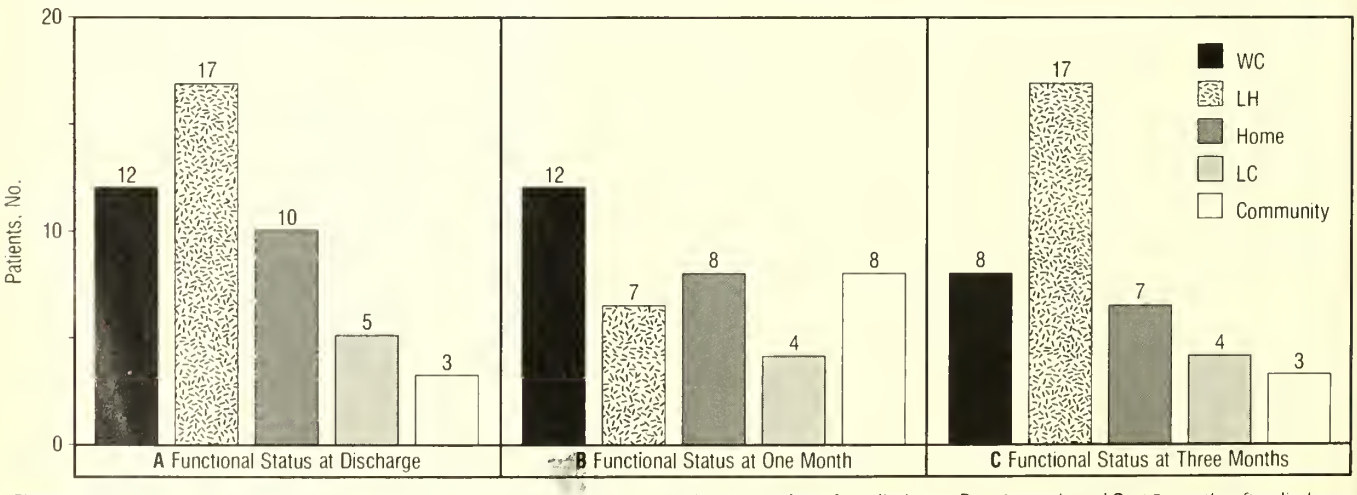

Figure 3.—The functional status is shown for 47 patients with bilateral lower extremity amputations, **A**, at discharge, **B**, at 1 month, and **C**, at 3 months after discharge from inpatient rehabilitation; 8 patients were lost to follow-up. LC = limited community ambulation, LH = limited home ambulation, WC = wheelchair only

of discharge, 12 were dependent on a wheelchair for all mobility, while 10 attained a household level of ambulation. Only 8 achieved community ambulation of some level (Figure 3-A).

At the one-month follow-up, most patients were at the wheelchair level of function, with the other patients evenly scattered among the other categories. Further analysis of the data revealed that of those patients at a limited household level of ambulation at the time of discharge, 7 (41%) maintained their level of function and 6 advanced to the household level; 8 patients were lost to follow-up (Figure 3-B).

At the three-month follow-up, those patients who were previously walking at a limited household level regained this level. Most patients achieved limited household ambulation at three months (Figure 3-C).

The patients who were functioning at a higher level at the time of discharge were noted to maintain or improve their level of functioning over the three months. Those patients discharged at a wheelchair level were either lost to follow-up or remained at the wheelchair level. Few (3, or 8%) of these advanced to walking at some time in the three-month period.

Of the 17 patients with bilateral below-knee amputation (Figure 4), 6 (35%) achieved limited household ambulation at the time of discharge; of these, at the one-month follow-up some had maintained function but others declined. By three months, however, these patients had advanced to household

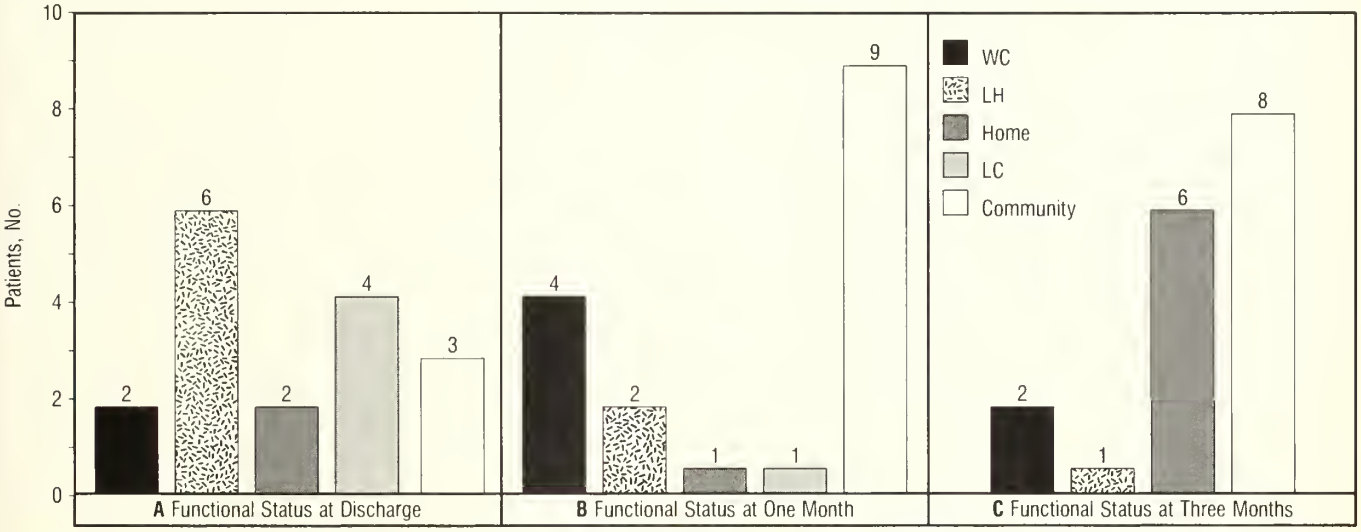

Figure 4.—The functional status is shown for 17 patients with below-knee/below-knee amputations, **A,** at discharge, **B,** at 1 month, and **C,** at 3 months after discharge from inpatient rehabilitation. LC = limited community ambulation, LH = limited home ambulation, WC = wheelchair only

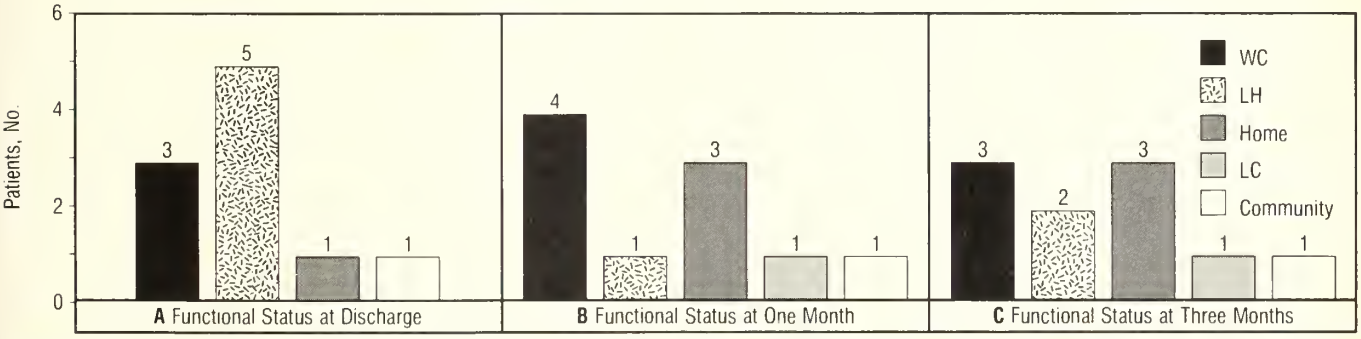

Figure 5.—The functional status is shown for 10 patients with above- and below-knee amputations, **A,** at discharge, **B,** at 1 month, and **C,** at 3 months after discharge from inpatient rehabilitation. LC = limited community ambulation, LH = limited home ambulation, WC = wheelchair only

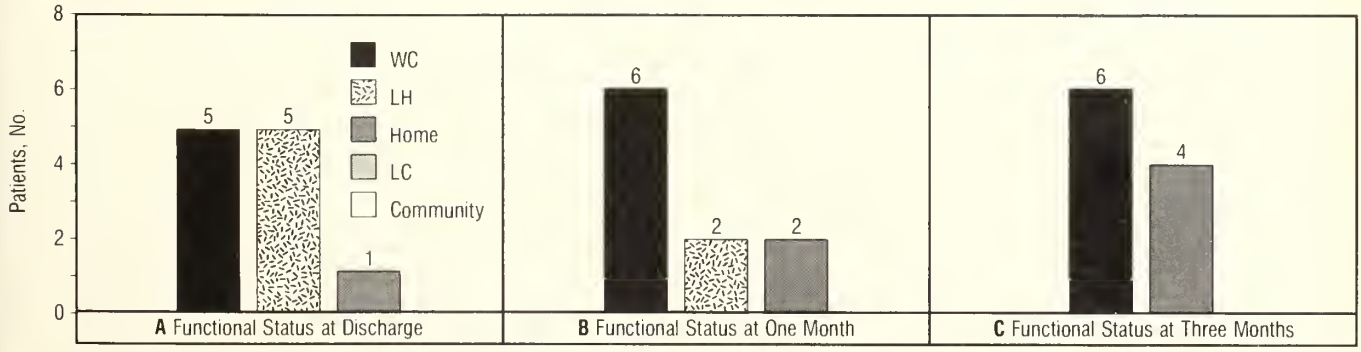

Figure 6.—The functional status is shown for 11 patients with bilateral above-knee amputations, **A,** at discharge, **B,** at 1 month, and **C,** at 3 months after discharge from inpatient rehabilitation (1 patient lost to follow-up). LC = limited community ambulation, LH = limited home ambulation, WC = wheelchair only

walking and even limited community walking. Those patients achieving on discharge a high level of functional mobility were able to attain and maintain limited community and community ambulation during the three months.

Similarly, persons with below- and above-knee amputations (Figure 5) achieved limited household mobility on discharge and advanced to household walking, with few advancing to limited community and community ambulation; about a third remained at the wheelchair level.

Although most of the patients with above-knee amputations were independent at the wheelchair level at the time of discharge (Figure 6), some achieved a limited household level of walking and maintained this up to three months after discharge.

Conclusion

A review of the rehabilitation literature failed to elicit any recent information regarding the functional mobility outcomes of patients with bilateral lower limb amputations.

In this limited study, we found that persons with bilateral lower limb amputations deserve a comprehensive rehabilitation program to attain (and maintain) goals of limited household walking. Further studies should examine the role concurrent disease plays in determining the appropriateness for prosthetic management; the cost-effectiveness; and the long-term benefits, both physical and psychosocial, of attaining the highest possible functional level.

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REHABILITATION MEDICINE Adding Life to Years

Stroke Rehabilitation: A Model Predicting Return Home

DAVID B. WILSON, MA; DENISE M. HOULE; *and* ROBERT A. KEITH, PhD, *Pomona, California*

We undertook this study to describe the changes in functional status for patients in a rehabilitation program for acute stroke and to identify the variables that best predict discharge home. Of 282 patients, 75% were discharged home. Increases in functional status were found for all 18 activities of the Functional Independence Measure from admission to discharge. Significant predictors of discharge disposition in a logistic regression model were the admission and discharge functional status scores, length of stay, and living arrangement before the stroke. The functional status at discharge was the most important predictor. Knowledge of these predictors can contribute to more appropriate treatment and discharge planning.

(Wilson DB, Houle DM, Keith RA: Stroke rehabilitation: A model predicting return home, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:587-590)

Stroke is the most common life-threatening neurologic disease and the third leading cause of death in the United States, after heart disease and cancer.[1] The American Heart Association has estimated that there are 500,000 new cases of stroke each year and a prevalence of nearly 2 million survivors.[2] The cost of care plus the loss of earnings has been estimated at $7.4 to $11.2 billion a year in the United States.[3] Medical rehabilitation reduces the economic and social burden of caring for stroke survivors with severe physical and mental impairment by reducing disability and enhancing social functioning.[4]

The focus of stroke rehabilitation is to increase patients' independence despite impairment. Accordingly, patient progress and the results of rehabilitation are assessed by functional status measures. The most frequently used outcome measures are self-care skills, followed by physical function, psychiatric cognition, and communication.[5] Other skills such as social functioning, memory and cognition, bowel and bladder incontinence, sexual functioning, and vocational issues may also be addressed by some measures. The assumption underlying the measurement of functional status is that proficiency in the activities measured is related to the amount of assistance required and to whether a person can function at home.[6]

Stroke outcome research has sought to identify characteristics and prognostic indicators that predict survival, discharge disposition, length of hospital stay, functional status, and neurologic status. This literature has been criticized for inconsistent methods and measures, making comparisons of findings across studies difficult.[7-9] Despite these limitations, review of these studies suggests that a previous stroke, coma from the start of the stroke, bowel and bladder incontinence, perceptual-spatial deficits, and neglect or denial syndrome are inversely related to functional status. Less favorable results have also been attributed to delays between onset and admission,[10,11] although more recent studies have not confirmed this relationship.[8] No clear relationship has been established between age, sex, or hemisphere of stroke and functional outcome. Functional score at admission has also been found to be positively correlated with functional end points[7]; the presence of a spouse seems to be positively related to discharge home.[8]

The purpose of the present study was twofold. First, it described changes in functional status for patients in a comprehensive stroke rehabilitation program. Second, indicators that predicted discharge home were identified. The goal was to enhance our understanding of the factors that influence discharge disposition to facilitate service planning for stroke survivors.

Patients and Methods

Data were collected for a 20-bed inpatient stroke unit from April 1989 through December 1990. This unit is part of a 64-bed, free-standing rehabilitation hospital. There were 309 consecutive admissions of stroke patients; 12 nonhemiplegic patients and 15 patients for whom functional status data were incomplete were excluded, resulting in 282 cases available for analysis. Patient information collected included age, sex, marital status, race, onset-admission interval, primary diagnosis, and living arrangement at admission and discharge. Functional status ratings were completed by treatment staff at admission and again just before discharge.

Functional status was measured using the Functional Independence Measure (FIM).[12] The 18 FIM items are grouped into six subscales: self-care (eating, grooming, bathing, dressing upper body, dressing lower body, and toileting); sphincter control (bladder management, bowel management); mobility (transfers between bed, chair, or wheelchair; toilet; tub or shower); locomotion (walking or wheelchair, stairs); communication (comprehension, expression); and social cognition (social interaction, problem-solving, memory). Each item is rated on a 7-point scale: 1, total assistance; 2, maximal assistance; 3, moderate assistance; 4, minimal assistance; 5, supervision; 6, modified independence; and 7, complete independence. The FIM was developed for the Uniform Data System for medical rehabilitation to establish a national data base with a consistent set of measures. The Uniform Data System is investigating the reliability and validity of this instrument.

Treatment was carried out in a self-contained stroke unit.

From the Research and Planning Center, Casa Colina Hospital for Rehabilitative Medicine, and the Claremont Graduate School, Pomona, California.
Reprint requests to Robert A. Keith, PhD, Casa Colina Hospital, 2850 N Carey Ave, Pomona, CA 91767.

TABLE 1.—*Functional Independence Measure Scores at Admission and Discharge (n = 282)**

Variables	Functional Independence Measure: Admission Mean†	Admission SD	Discharge Mean†	Discharge SD
Self-care				
Feeding	3.44	1.55	4.98	1.49
Grooming	3.63	1.49	4.97	1.62
Bathing	2.82	1.63	4.01	1.71
Dressing (upper)	3.12	1.48	4.62	1.80
Dressing (lower)	2.89	1.53	4.19	1.84
Toileting	2.76	1.53	4.17	1.86
Sphincter control				
Bladder	2.73	1.74	4.42	1.95
Bowel	2.98	1.92	4.55	1.77
Mobility (transfers)				
Bed, chair, wheelchair	3.09	1.64	4.35	1.64
Toilet	2.85	1.49	4.20	1.77
Tub	2.77	1.49	4.02	1.60
Locomotion				
Walking or wheelchair	2.38	1.43	4.19	1.78
Stairs	1.71	1.42	2.90	2.00
Communication				
Comprehension	3.16	1.82	4.09	2.00
Expression	3.18	1.86	4.00	2.06
Social/cognition				
Social interaction	3.54	1.87	4.29	1.88
Problem solving	2.99	1.78	3.84	1.81
Memory	3.19	1.86	4.02	1.84

*See text for an explanation of scoring.

†All mean differences between admission and discharge are statistically significant at $P < .01$, adjusted for multiple analyses using the Bonferroni method.

The treatment team comprised a physiatrist, a program manager, and therapists from the following disciplines: physical therapy, occupational therapy, speech, recreational therapy, psychology, and social work.

Patient Population

There were 135 men and 147 women with approximately equal numbers with left and right hemiparesis. In all, 68% of the patients were white, 15% were Hispanic, 4% were African-American, 2% were Asian, and the remaining 11% were not classified. The average age was 69 years, with a range from 15 to 90. The majority of the patients (61%) were married, 29% were widowed, 5% were divorced, 4% were single, and 1% were separated. Of these patients, 91% were living with family or relatives or alone before their stroke.

Most of the patients, 94%, were admitted for rehabilitation for the first time, and 6% were readmissions. Accordingly, 89% were admitted from an acute care facility, 6% from skilled nursing facilities, 4% from home, and 1% from other living arrangements. The mean length of time between the stroke and the admission for rehabilitation was 22 days. The mean length of stay was 31 days.

Results

Functional Status Results

The patients showed pronounced improvement in functional status from admission to discharge. The mean levels of functional status at admission and discharge for each of the 18 FIM items are reported in Table 1. An overall mean score of 2.96 across the 18 items at admission indicated that the patients required moderate to maximum assistance for each of these tasks. The lowest mean level of functioning at admission was 1.71, for ability to climb stairs, indicating that most patients were either unable to perform this task or required maximal assistance. The highest mean level of functioning at admission was for grooming and social interaction (3.63 and 3.54, respectively), with only moderate assistance required by the average patient.

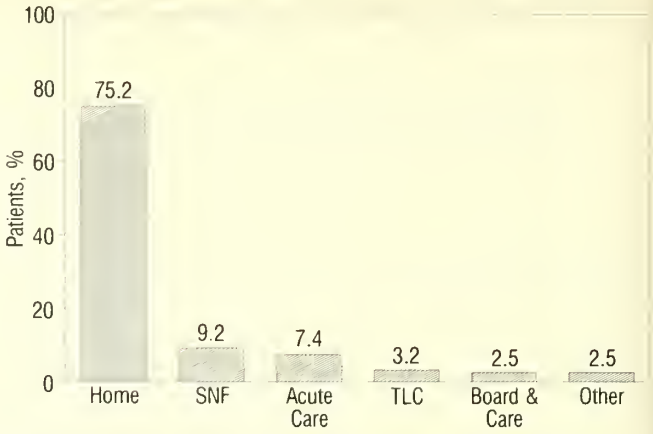

Figure 1.—The graph shows the discharge destination of 282 patients who underwent rehabilitation after a stroke. SNF = skilled nursing facility, TLC = transitional living center

At discharge, all but 2 of the 18 items had a mean score above 4, which reflects a minimal level of assistance required to perform the tasks. Patients continued to require a high level of assistance for climbing stairs and problem solving. The mean scores for these tasks were 2.90 and 3.84, respectively. A multivariate repeated measures analysis of variance indicated a significant difference between a linear composite of the 18 FIM admission and discharge items ($F[18, 264] = 44.00$, $P < .0001$). Univariate t tests further showed that the discharge mean was significantly higher than the mean admission score for each of the FIM items ($P < .01$).

Who Goes Home?

As shown in Figure 1, the majority of patients in this study, 75%, were sent home. To identify those characteristics that predict return home, a logistic regression analysis was done, with home versus not home as the dichotomous dependent variable.

Variables commonly cited in the stroke literature as predictors of outcome were used in the first logistic regression model. The predictor variables were age, sex, side of hemiplegia, length of stay, onset-admission interval in days, marital status (married = 1, not married = 0), living arrangement before stroke (home = 1, not home = 0), total FIM score at admission, and total FIM score at discharge. Age, sex, marital status, onset-admission interval, and side of hemiplegia did not contribute significantly to the prediction of discharge disposition.

The second logistic regression model tested included only the significant variables from the first analysis: total FIM score at admission, total FIM score at discharge, living arrangement before stroke, and length of stay. The results from this logistic regression model are presented in Table 2. This model correctly classified the discharge disposition of 83% of the patients. The model was a significant improvement over the null model ($\chi^2[4] = 78.1$, $P < .001$), which would predict that all patients return home and thus correctly classify 75%. The classification table (Table 3) shows that the model successfully predicts 96% of those patients who return home but only 59% of those patients who do not return home. Comorbidity, a factor not included in the

TABLE 2.—*Logistic Regression Analysis Predicting Return Home*

Variable	*B*	*95% Confidence Interval*	*Odds Ratio*
Admission FIM score	0.02*	0.004-0.04	1.02
Discharge FIM score	0.03†	0.01-0.04	1.03
Previous living arrangement	1.71†	0.72-2.70	5.51
Length of stay	0.05†	0.02-0.07	1.05

FIM = Functional Independence Measure

*$P < .05$.
†$P < .001$.

TABLE 3.—*Classification of Predictions From Logistic Regression*

Observed	*Predicted* Home	*Predicted* Not Home	*Correct Prediction, %*
Home	197	15	93
Not home	32	38	54
Overall	229	53	83

model, may account for why the model is less successful in predicting those who do not return home. Patients discharged to an institutional setting commonly have more medical complications.

To facilitate interpretation of the logistic regression, the mean scores for admission FIM, discharge FIM, and length of stay by discharge disposition are presented in Figure 2. Patients who returned home had higher functioning as measured by the total FIM score at admission (56.4 versus 43.6) and discharge (82.1 versus 56.9). Patients returning home also remained in rehabilitation longer (32.8 compared with 23.1 days). This may reflect a tendency to keep longer the patients who seem to have more promise for functioning successfully at home. Of the patients discharged home, 95% had lived at home before their stroke, compared with 83% of the patients who did not return home.

Discussion

The efficacy of intensive rehabilitation for stroke after the acute phase of medical care has been shown by a series of randomized controlled studies based on the population of Edinburgh, Scotland.[13,14] Functional independence at discharge was greater for those in the stroke unit, and their length of stay was shorter.[13] Two additional population-based controlled trials compared special stroke rehabilitation units with general medical wards and found a higher percentage of persons living at home at 3 and 12 months after onset.[15,16] These randomized trials indicate that specialized rehabilitation treatment leads to gains that are not explained by spontaneous recovery.[17]

The Framingham study is a longitudinal study in which 148 long-term stroke survivors in a Massachusetts town were observed beginning in 1948.[18] This investigation found that 78% of stroke survivors were independent in ambulation six months or more after their stroke. Furthermore, 68% were independent in activities of daily living, and 85% were living at home. These studies substantiate the potential for recovery from stroke and the contribution that rehabilitation can make in the recovery process.

The current study indicates that substantial gains occurred during rehabilitation. At admission, most patients required moderate to maximal assistance on all 18 activities assessed by the Functional Independence Measure. The average level of assistance required by patients at discharge had decreased to between moderate and minimal assistance for all tasks but climbing stairs and problem solving. These levels allowed patients to live at home with the help of relatives or friends.

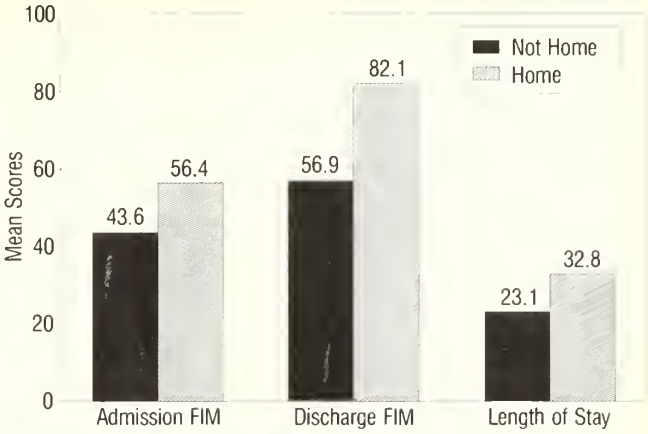

Figure 2.—The functional status and length of hospital stay as they relate to discharge disposition are shown by mean Functional Independence Measure (FIM) scores.

The logistic regression model accurately predicted discharge disposition for 83% of the patients. Factors related to discharge home were higher patient functioning at admission and discharge, longer rehabilitation stays, and living at home before the stroke. Age, sex, marital status, onset-admission interval, and side of hemiplegia did not make independent contributions to the prediction of discharge disposition. Although Kelly-Hayes and co-workers reported that the occurrence of institutionalization increased with age for women,[19] our finding was that age was not related to discharge status. DeJong and Branch showed that marital status was the most important predictor of living arrangement, particularly for men.[20] Likewise, Kelly-Hayes and associates found support for an interaction between sex and marital status on return home, with the presence of a spouse being significant for men but not women.[19] The nonsignificance of marital status in the present study may be attributed to a selection bias toward admitting patients with a spouse or other relatives with whom they may live. The findings with respect to sex, onset-admission interval, and side of hemiplegia are consistent with those reported elsewhere.[19,20]

A comparison of the results with similar logistic regression analyses is limited because success rates for predicting living arrangement were not reported.[19,21] The importance of functional status, however, is consistent with the prediction models tested by other researchers,[19-21] underscoring the value of functional assessment measures in stroke outcome research.

This study suggests that in addition to functional status, living arrangement before a stroke is an important indicator of patients' potential to benefit from rehabilitation. These characteristics can help provide a basis for rational planning for stroke survivors.

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ABOUT AGING—READING *YOUR* LIPS

I'm going to a lip-reading class on Monday afternoons, and I'm the dumbest member of the class.

My chauffeur and mentor, Oliver, takes me in his car, and then wishes he could persuade the members of the class that he doesn't know me. I get silly. It's not right and I've got to stop, but a lot of it just strikes me as funny. It isn't.

There we sit, maybe six men and three women. We face each other, behind tables arranged in a semicircle, and every eye is on the attractive teacher, Mrs Callaway. Now, she's something else; she comes from 14 years at Loma Linda, and the audiologists there give her top rating in teaching lip reading. She's about the age of our oldest granddaughters, maybe. There she goes, waving her hands, walking up and down in front of us, and talking without making a sound. Her body language, which is part of lip-reading techniques, plainly says, "I'm working at this—read my lips!" There we sit, eyes glazed, focusing on her face, furrowed brows with bifocals slipping down our noses, mouths slightly open so we can concentrate better—and everybody but me gets what she's saying.

Oliver again: We share a disability, but he is grimly determined to turn his into an asset. I don't quite know what I want, or didn't, until I learned that this type of class requires a lot of concentration, and if you can manage that, you won't be as likely to deteriorate mentally.

I needed to hear that. It's a cogent argument. Mrs Callaway talks her silent language to each of us in turn, and I watch each student. Sometimes I can get the student's silent response—those are the times Mrs Callaway gives me a gold star. Not often. You see, my problem is not so much with sound as it is with separating words; if you're a fast talker, you might as well be talking Choctaw for all I'd know. You see, deafness is a two-way street; the speaker has to do his or her part, too; I've seen occasions when it was the speaker causing the problem for the deaf listener. And speakers begin to wonder if their uppers are falling down when the deaf person keeps looking at their mouth instead of their eyes. Well, as for that—you'll never learn to lip-read by looking at the speaker's eyes. Relax.

My good friend Mary is deaf but lip-reads like a dream; she sits in church and during the sermon visits with a deaf friend across the aisle.

I must get down to concentrating, mind my manners, and not bother Oliver. No horsing around. Read their lips.

JOSEPHINE SMITH
Claremont, California

Born in 1899, Mrs Smith writes a column, "About Aging," for the *Claremont Courier*, Claremont, California. She retired from teaching creative writing in 1989—except for a few "old" students. Reprinted with permission. She was recently honored by the California Newspaper Publishers Association with a first-place prize for columns published in a newspaper of between 3,500 and 13,000 circulation—one of the most competitive divisions.

REHABILITATION MEDICINE: Adding Life to Years

Reversing Disability of Irreversible Lung Disease

BRIAN L. TIEP, MD, *Pomona, California*

Pulmonary rehabilitation is a comprehensive multifaceted team approach for integrating medical management, coping skills, self-management techniques, and exercise reconditioning. It provides patients with chronic lung disease the ability to adapt and live full and nearly normal lives. These changes are possible because the overall disability includes significant reversible components: Patients have bronchospasm, infection, and cor pulmonale; they respond to progressively impaired lungs by progressive inactivity, leading to physical deconditioning. Both factors contribute to dyspnea. Because patients naturally fear dyspnea, they panic easily. During panic, their work of breathing may increase and respiratory failure may result. Pulmonary rehabilitation provides good medical management; provides exercises to increase strength, endurance, and tolerance to dyspnea; and trains patients in panic control. These programs have not been shown to lengthen life span or improve static lung function. They increase exercise performance and render patients functional, independent, and subject to fewer hospital admissions. Pulmonary rehabilitation is the only approach to chronic lung disease short of lung transplantation that improves the long-term outlook for these patients.

(Tiep BL: Reversing disability of irreversible lung disease, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:591-597)

The therapeutic approach of pulmonary rehabilitation is now more than 25 years old. Its foundation is to provide patients with chronic lung disease the ability to adapt and live a full and nearly normal life-style despite the ravages of irreversible disease. Pulmonary rehabilitation is administered by a team of medical and paramedical professionals and uses exercise, therapy, psychology, and many other modalities to reverse the disability imposed by the irreversible impairment of chronic lung disease. The logic of the approach comes from considering the full etiology and nature of disability. The most disabling component of deterioration from chronic obstructive pulmonary disease is the manner in which the patient naturally succumbs to lung impairment. The patient becomes accustomed to living a disabled life-style. Pulmonary rehabilitation has a solid physiologic and psychological basis; moreover, the alternative is progressive disability, dependence, and revolving door hospital admissions for exacerbations.

Chronic Lung Disease

The most common of the chronic lung diseases is chronic obstructive pulmonary disease (COPD), an aggregate of lung conditions that appear in varying proportions and are characterized by the inability to move air freely through the airways. Chronic obstructive lung disease encompasses emphysema, chronic bronchitis, and adult asthma.[1] In emphysema there is irreversible lung destruction particularly at the alveolar level; chronic bronchitis involves inflammation and chronic infection of the airways. Asthma is an inflammatory condition characterized by airway hyperreactivity. Emphysema and chronic bronchitis are almost always caused by smoking, and asthma is frequently exacerbated by exposure to it. Patients with cystic fibrosis and the restrictive lung diseases such as interstitial pulmonary fibrosis and kyphoscoliosis also respond to rehabilitation.

Energy Crisis

Persons with normal lungs have a wide safety margin between their ability to perform gas exchange and their bodies' requirements at rest. They require about 1% to 2% of their oxygen to supply the demands of their respiratory musculature, whereas patients with chronic lung disease may require up to 50% to 60%. In actuality, they maintain little or no reserve between quiet breathing and ventilatory decompensation. A minor respiratory tract infection or even a panic episode that reduces a patient's breathing efficiency can precipitate a major crisis. Patients are commonly admitted to hospital for an exacerbation induced by a panic episode.

How Can Pulmonary Rehabilitation Help?

While the disease of emphysema is irreversible, there are several reversible components to the overall clinical disorder. Bronchospasm, inflammation, and infection are manageable by medication and life-style changes.[2-6] Physical deconditioning, which is part of the disability, is reversible by an exercise program. Panic is controllable by anxiety-reducing measures and the rehabilitation program in general.

The Pulmonary Rehabilitation Program

Pulmonary rehabilitation requires a comprehensive multifaceted team approach for integrating medical management, coping skills, self-management techniques, and exercise reconditioning. The team commonly comprises a pulmonologist, nurse specialist, respiratory therapist, occupational therapist, physical therapist, social worker, dietitian, psychologist, and clinical pharmacist. Each team member is treated as a colleague and contributes to goal planning and clinical decision making.[5,6]

A unique concept is that patients are included as team members for their own program. As such, they assume a major role in their care. After the program, they will be in

From the Casa Colina Hospital for Rehabilitative Medicine, Pomona, California.
Reprint requests to Brian L. Tiep, MD, Medical Director, Pulmonary Rehabilitation, Casa Colina Hospital for Rehabilitative Medicine, 255 E Bonita Ave, Pomona, CA 91767.

ABBREVIATIONS USED IN TEXT

COPD = chronic obstructive pulmonary disease
MDI = metered-dose inhaler

charge as an extension of the physician and pulmonary rehabilitation team. Family members also occupy an important role in the rehabilitative process. Patients and their families are taught how to interact so that the patient achieves some level of independence while preserving family support. Families are also encouraged to maintain smoke-free home environments.

Patient Screening

Patients are typically referred for rehabilitation following an exacerbation. Their evaluation includes a history and physical examination, lung function tests, arterial blood gas measurements, chest x-ray study, electrocardiogram, and other appropriate studies. Their forced vital capacity and forced expiratory volume in one second are usually less than 55% of predicted, and they are functionally disabled by their diseases. They must be motivated to participate in the difficult task ahead, and they should be nonsmokers at the time of admission to the program.[2-6]

The Program

The clinical emphasis for chronic lung disease is the term "chronic." A patient will live with lung disease for the rest of his or her life. Pulmonary rehabilitation is the means of guiding an enhanced life-style and self-image. Patients entering pulmonary rehabilitation programs are usually sedentary nonparticipants in life. They are limited by their fear of dyspnea, panic, and physical deconditioning and by their lung disease. The first task of the rehabilitation team in reversing the spiral of disability (Figure 1) is to convince the patient that dyspnea, although uncomfortable, can be tolerable and that it is not life-threatening. The next task is to set goals that serve as the impetus to effect and sustain the rehabilitative process.[4-6]

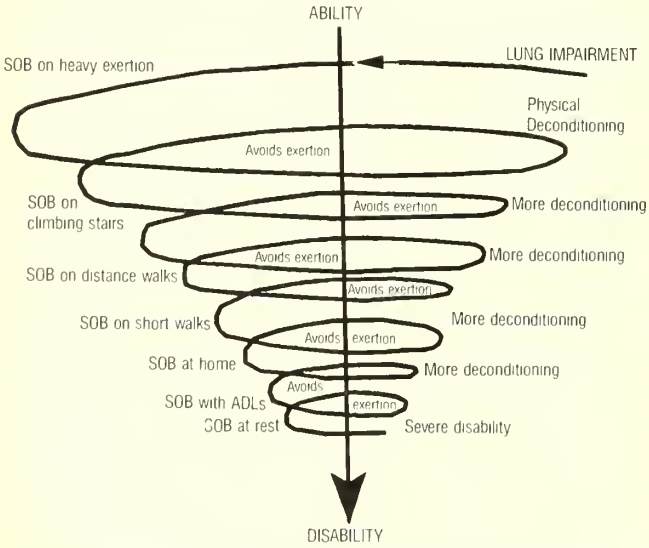

Figure 1.—The downward spiral of disability is depicted: As a patient experiences dyspnea during exertion, he or she begins to evade the discomfort by avoiding activity. This leads to physical deconditioning, which leads to progressive inactivity. Eventually the patient is inactive and rendered dyspneic from performing self-care. ADLs = activities of daily living, SOB = shortness of breath

Rehabilitation programs are often highly structured albeit tailored to meet the needs of an individual patient. Patients learn about their lungs, how their lung disease affects them, and the means of managing their lives to reduce the disability. The multifaceted features of the program are integrated into a package that enables the patients and their families to effectively modify their life-styles to meet their collective needs.

Patients who have long been sedentary do not immediately take to an active program. They must become immersed in the rehabilitative process to gain the necessary self-confidence. For patients to achieve a self-image as active people, they must assume that role and begin experiencing it.

Exercise Program

Although patients with chronic lung disease have a limited ability to gather oxygen, physical deconditioning imposes further limitations on oxygen transport to the muscle cells. The lungs are only the first step in the process leading to gas exchange at the tissue level. Upper and lower extremity exercise programs build strength and endurance as they improve oxygen transport and use in those muscles.[7,8]

The exercise programs begin by convincing the patient to tolerate dyspnea rather than to fear it. As this major hurdle is overcome, the patients often show a surprisingly rapid improvement in performance as their full capabilities are realized.[9,10]

Walking is an ideal exercise for most patients because it improves mobility and independence (Figure 2). It is a submaximal exercise for many, but walking at any speed is a major effort for patients with severe cardiopulmonary impairment. Bicycle ergometry exercises a different set of muscles and is non-weight-bearing; it may not be as beneficial as walking. Bicycle ergometry is useful during inclement weather, however, and offers an exercise vehicle for those patients who are unable to walk.[7]

Figure 2.—This patient is on his walking program while being monitored by a physical therapist. Walking is the best cardiovascular exercise for these patients as it also improves patient mobility. He is wearing a Pendant oxygen-conserving cannula.

Upper extremity exercise training is important for improving patients' ability to do self-care and personal hygiene. These patients typically have dyspnea when they elevate their arms above shoulder level.[11] This limits such self-care functions as brushing teeth, washing hair, and, for men, shaving. Upper extremity exercise training (Figure 3) is initiated by arm bicycle ergometry with protocols directed for both strength and endurance. Patients are also taught gravity-resistive arm exercises (Figure 4), which are repetitive upper extremity efforts against the force of gravity, to continue their strength and endurance training at home.

Ventilatory Muscle Training

Over the past 12 to 15 years, there has been mounting interest in ventilatory muscle exercise. The three approaches to ventilatory muscle training are isocapneic hyperpnea, which selectively builds endurance; inspiratory resistance training, which selectively builds strength; and inspiratory threshold training, which builds both, depending on the training protocol. In isocapneic hyperpnea, patients hyperventilate into a tube that returns some of the expiratory carbon dioxide to the patient to prevent respiratory alkalosis. In inspiratory resistance training, the patient inspires against

Figure 3.—These patients are performing their arm bicycle ergometry while being monitored by an occupational therapist and assistant. Strength and endurance in the upper extremities help patients carry out their activities of daily living.

Figure 4.—These patients are performing their gravity-resistive exercises, which are arm exercises to build and maintain upper extremity strength and endurance, and which serve as the home program replacement for arm ergometry.

Figure 5.—This patient is performing her inspiratory muscle threshold training. This device can be set to a specific threshold resistance and can improve strength and endurance in the inspiratory muscles.

specific workloads. In inspiratory threshold training, the patient must exceed a specific inspiratory pressure threshold to release the flow of air (Figure 5). By this method, training protocols can be specified to favor endurance, strength, or both. Although ventilatory muscle strength and endurance are increased by these specific exercises, it is not clear whether ventilatory muscle training adds any benefit beyond the other exercises in pulmonary rehabilitation programs.[12-15]

Training in Activities of Daily Living

Activities of daily living include all of the usual requirements for independent living, such as self-care, management of the home environment, work, and leisure activities. Training in these activities includes learning to pace activities and economize on excessive body movements until a more normal life-style can be resumed. This training is supported by the upper and lower extremity exercises, breathing retraining techniques, and relaxation for self-control and pacing. Patients learn to establish priorities for their activities so that they can strike a reasonable balance between what must be done and the activities that add quality to their lives despite the extra effort and within the limits of their lung impairment.

The basic philosophy of training in the activities of daily living is for patients to be able to minimize the energy cost of such essential activities as grooming, hygiene, preparing meals, and maintaining environmental neatness and cleanliness, while leaving room for quality-of-life activities (Figure 6). Patients completing pulmonary rehabilitation programs are encouraged to return to some of their favorite leisure pursuits, which often include golfing, bowling, traveling, volunteering, and other personal-involvement leisure activities. Some patients are also able to return to part-time or full-time work.[16]

Patients learn breath control during daily activities such as self-care, household chores, marketing, yardwork, lifting and proper body mechanics, relaxation techniques, and panic control. Training sometimes includes the activities themselves while teaching a means of accomplishing them most comfortably and by incorporating breathing retraining techniques. They learn to shop while carrying oxygen and pushing a cart, to shower and prepare meals while seated, make their beds with economy of movement, and groom themselves while seated in front of a mirror.

Many patients with chronic lung disease describe severe dyspnea when they are frightened, angry, or frustrated. They are taught relaxation and breathing retraining techniques to control these situations. This training consists of the progressive relaxation of muscle groups in a modified Jacobsonian procedure. Relaxation training often helps patients to get to sleep without the use of medication.

Claustrophobia associated with anxiety is a common incapacitating problem for patients with chronic lung disease. A patient becomes intolerant of crowds. He or she may be unable to shower because of the feeling of confinement. Patients are taught to counteract these feelings by learning to take charge, using breathing retraining techniques such as pursed-lips breathing and progressive muscle relaxation techniques.[4-6]

Many patients experience exacerbations of their breathing problems with exposure to the fumes or aerosolized chemical droplets of everyday household cleaners or to perfumes and colognes. They are encouraged to avoid these chemicals if possible or to change the method of use so as to minimize exposure to their lungs. Aerosols, pump sprays, fine powders, and products with strong fumes are similarly discouraged. Alternative products are discussed as well as the use of proper masks when exposure is unavoidable. Patients also learn to avoid or control factors such as sudden cooling and reflux esophagitis that lead to bronchial hyperreactivity. They learn to recognize specific allergens (where appropriate) and to avoid them. Patients are also taught how to use assertion techniques to deal tactfully with others who are smoking or using other toxic airborne products around them.

Insomnia

Patients with chronic lung disease often suffer from insomnia for a variety of reasons: dyspnea, orthopnea, anxiety, or depression. In none of these instances are sedatives or tranquilizers advisable as they are often ineffective and tend to depress the respiratory drive. Thus, the reasons for insom-

Figure 6.—This patient is learning efficient ways of preparing meals in the kitchen of the rehabilitation program.

nia should be addressed. Bronchospasm and congestive heart failure should be treated and anxiety and depression managed. The daily exercise program itself may relieve anxiety while distracting the patient's attention from the disease. Better nutrition may also facilitate better patterns of sleep. Relaxation training can be helpful, along with other techniques such as reading or watching television using a sleep timer.[6]

Medications

Patients often enter the pulmonary rehabilitation programs with a long list of medications. Many of these are bronchodilators and anti-inflammatory agents, but some are cardiac medications or drugs for the gastrointestinal tract. The list can be long, and compliance probably decreases as more medicine is added. It is thus the task of the rehabilitation team to help a patient understand and take the medication properly. Patients should carry around a medicine list at all times and have an extra supply in case they are detained. Patients should keep records and chart their medication use.[2-6]

The most commonly used medications are in the bronchodilator class. Irrespective of whether a patient demonstrates bronchodilator reversibility on pulmonary function tests, most patients are improved symptomatically by their use.

Corticosteroids are potent anti-inflammatory agents with a particularly important role in the treatment of chronic bronchitis and asthma. They fight bronchial hyperreactivity and enhance the action of bronchodilators by increasing β-receptor responsiveness. Oral and intravenous steroids are most effective, but their profile of side effects has led to an increasing use of inhaled preparations.

The most frequent cause of an exacerbation of chronic lung disease is bronchopulmonary infection. The signs and symptoms become familiar to these patients and include increased dyspnea, increased coughing with expectoration of more copious purulent sputum, and cor pulmonale. Patients are often afebrile as they tend to be colonized with the organisms for some time before the infection. Sputum cultures are not always helpful; nonetheless, they should be done when serious infection is suspected. Antibiotic therapy is prescribed to help clear bacterial infections.

Patients with right-sided heart failure from cor pulmonale should have their hypoxemia corrected, particularly during exertion and sleep. Diuretics are useful in reducing the cardiac workload, but serum potassium levels should be monitored and, if necessary, corrected.

Mucokinetics are valuable in clearing airways. Water is the best agent, particularly in conjunction with bronchodilators and steroids. Iodinated glyceryl and acetylcysteine-guaifenesin help to thin secretions. Standard cough syrups may be of little or no value in this regard.

Nutrition

About 40% of patients with COPD have difficulty in maintaining adequate nutrition. The cause of the weight loss is not clear; perhaps it occurs because their appetites tend to be poor and the energy cost of breathing is usually excessive. A loss of protein and lean body mass leads to weakness of skeletal muscle, particularly in the diaphragm. Eating several small meals a day and taking food supplements have been tried and have met with varying degrees of success.[4-6]

It is generally advisable for patients to limit their sodium intake, especially if they have cor pulmonale. These patients should have adequate fluid intake, however, while avoiding the overhydration that could contribute to cardiac decompensation.

Respiratory Therapy

Respiratory therapy techniques are perhaps the most potent short- and long-term modalities in the management of patients with chronic lung disease. These techniques open and clear airways and relieve bronchospasm.

Nebulized bronchodilators. Nebulized medications are particularly effective in the treatment of the acute and chronic phases of COPD and bronchial asthma. And yet, their delivery is inefficient. The efficacy of this treatment is improved by teaching patients competent self-administration. Handheld nebulizers are as effective as intermittent positive pressure administration and safer. Metered-dose inhalers (MDI) are now replacing the nebulizers, being as effective and considerably less expensive. The self-administration of MDIs requires dexterity, aiming, and timing, however. Also, the pressurized aerosol shoots so rapidly that the droplets fail to make the turn at the back of the throat, causing impact and deposition there instead of along the airways. Most of these problems can be solved by devices known as spacers such as the AeroChamber or InspirEase. These are holding chambers into which a patient discharges the MDI and then slowly inhales. The airflow, being slower, tends to be more laminar, distributing droplets more evenly throughout the lower airways. The initial draw is timed to the beginning of inhalation, which further facilitates deeper penetration into the smaller airways.[17,18]

Chest physiotherapy. Patients with chronic lung disease often have great difficulty clearing their secretions. The use of postural drainage, percussion, and vibration along with augmented coughing helps to jar secretions loose. Again, patients should be well hydrated and bronchodilated for chest physiotherapy to be maximally effective.

Oxygen therapy. Many patients with severe chronic lung disease are unable to oxygenate their tissues sufficiently while breathing room air and thus require supplemental oxygen. Multicentered studies in the United Kingdom, the United States, and Canada have established that oxygen therapy for hypoxemic patients increases the length and quality of life despite the burden of having to carry the oxygen.[19,20] Because patient mobilization is critical to successfully conducting an active life-style, oxygen systems must be truly portable.[21]

When patients are first prescribed oxygen, they go through a series of changes in the concepts of themselves and their mortality. This is a delicate time for patients, and members of the team must devote their skill and quality time in helping these patients accept their need for oxygen.[21]

Oxygen is supplied in three forms: compressed gas, liquid, or oxygen concentrator. Compressed gas oxygen is stored in metal cylinders under high pressure (2,000 to 3,000 lb per in^2). An 8-kg (18-lb) system can supply 4.5 hours of oxygen at 2 liters per minute. Liquid oxygen is oxygen cooled to nearly absolute zero degrees, stored in a modified thermos, and containing more oxygen per unit volume and weight than compressed gas oxygen. A 4.3-kg (9.5-lb) system can supply eight hours of oxygen at 2 liters per minute. A great advantage of this system is that patients can easily and

Figure 7.—This patient is practicing his pursed-lips breathing technique designed to improve gas exchange. He is using the pulse oximeter as a biofeedback device to increase oxygen saturation.

safely transfer the oxygen from the reservoir to the portable unit.

An oxygen concentrator is an electrically powered device that extracts oxygen from room air at about 95% purity, depending on the flow. These are really stationary systems as they require wall current for their operation. A back-up oxygen cylinder is required for both portable use and in case of power failure.

Oxygen Delivery Systems

The standard oxygen delivery method over the past 30 years has been the dual-pronged nasal cannula. This has had good patient acceptance but wastes about 80% of the oxygen. Over the past six to seven years, newer devices have become available that deliver oxygen more efficiently. These include transtracheal catheters, reservoir cannulas, and electronic demand pulsing devices.[22]

Transtracheal catheters are small plastic tubes that are inserted through the neck and into the trachea. Oxygen flowing into the trachea improves the efficiency of oxygen delivery over standard nasal cannula by a factor of 2:1 to 3:1 because it bypasses upper airway dead space using the upper airways as a reservoir. It has cosmetic advantages and relieves nasal irritation.

The reservoir cannulas, the Oxymizer and the Oxymizer Pendant, function by storing oxygen during exhalation and making that stored oxygen available for the next inhalation. These are the simplest of the oxygen-conserving devices and improve the efficiency of oxygen delivery by 2:1 to 4:1 over continuous-flow delivery.

The electronic demand pulsing devices function by sensing the beginning of inhalation and delivering an early inspiratory oxygen pulse. These devices vary in their configurations, and they improve on the efficiency of continuous flow delivery by a factor of 2:1 to 7:1. Some units have apnea alarms and fail-safe mechanisms whereas others excel in lower weight, longer battery life, and greater efficacy. Most are stand-alone devices, but some are integrated into liquid systems or wall oxygen.

Breathing Retraining

Breathing retraining techniques have been the mainstay of many pulmonary rehabilitation programs. The most common techniques are diaphragmatic breathing and pursed-lips breathing. In pursed-lips breathing, the patient inhales more deeply and exhales more slowly through pursed lips. Exhaling through pursed lips slows the exhalation phase, which causes the person to maintain higher lung volume and prevents airway collapse. Pursed-lips breathing not only reduces dyspnea, it also improves gas exchange probably by improving ventilation-perfusion matching. Recently this technique has been taught with the aid of the pulse oximeter as a bio-

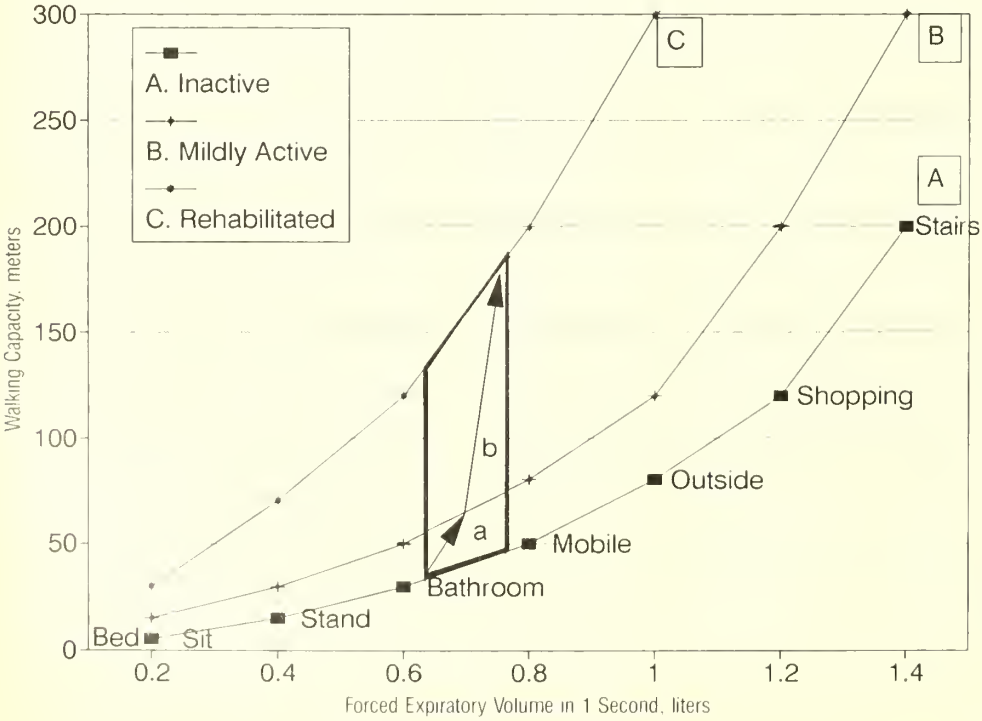

Figure 8.—This model shows how pulmonary rehabilitation relieves disability in patients with chronic lung disease. With similar forced expiratory volumes in 1 second (FEV_1), inactive patients are less functional (curve **A**). During the first 2 weeks of the program, they make rapid functional progress almost entirely from exercise (arrow **a**). With further rehabilitation, they become functional while showing little or no change in FEV_1 values (arrow **b**). If they remain active, they may remain functional between curves **B** and **C** but within the confines of the quadrangle. Changes in FEV_1 values probably represent reversible components.

feedback guide to increase oxygen saturation (Figure 7). Patients whose oxygen needs are borderline can sometimes circumvent their supplemental oxygen requirement by pursed-lips breathing biofeedback during exercise.[23-28]

Home Program

Pulmonary rehabilitation in the hospital setting is the beginning of a life-pattern change. Hence, a patient discharged from the program is provided with a home program to continue rehabilitation independently. Long-term follow-up is the best assurance of long-term success. The team monitors the progress of the patient through return outpatient visits. Also, the patient participates in "better breather clubs," which are patient support groups cosponsored by the pulmonary rehabilitation program and the local chapter of the American Lung Association.[6]

Pulmonary Rehabilitation in Perspective

With the multiple facets of pulmonary rehabilitation, what should be the expectation of a patient? Although the initial cause of disability was lung impairment, as the disease process slowly progressed, the patient became increasingly physically deconditioned. Thus, there are now two problems: lung disease and physical deconditioning. In Figure 8, an attempt is made to show the relative nature and reversibility of these two causes of disability. As depicted in the graph, most of the effects of rehabilitation are brought about by the exercise program, with a relatively smaller contribution from improvement in pulmonary mechanics.

Thus, despite having irreversible disease, patients with COPD and restrictive lung diseases can benefit substantially from pulmonary rehabilitation. They learn to accept and tolerate dyspnea and the reality of their disease while not dwelling on its limitations. They overcome anxiety and depression while building endurance, strength, and confidence and thus become more independent and mobile.

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Exercise Testing and Training in Patients With Peripheral Vascular Disease and Lower Extremity Amputation

MICHAEL PRIEBE, MD; GARY DAVIDOFF, MD; *and* RICHARD M. LAMPMAN, PhD, *Ann Arbor, Michigan*

Patients with peripheral vascular disease have a high risk of coronary artery disease. The risk is even greater when the peripheral vascular disease leads to lower extremity amputation. Exercise testing using lower extremity exercise has been the "gold standard" for screening for coronary artery disease, but many patients with peripheral vascular disease and those with amputations have difficulty doing this type of exercise. Arm exercise ergometry has been shown to be a safe and effective alternative for the detection of coronary artery disease in patients who cannot do leg exercise. This test has also been used to determine safe exercise levels and may be able to predict the ultimate level of prosthetic use in amputees. Exercise training with arm ergometry also improves cardiovascular efficiency and upper body strength in poorly conditioned patients. Studies are needed to appreciate fully the role of exercise testing and training in the recovery of these patients after amputation.

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Patients with peripheral vascular disease (PVD) have a high prevalence of coronary artery disease.[1-4] Patients who require peripheral revascularization are at an increased risk for cardiac complications including silent ischemia, myocardial infarction, arrhythmia, and death from coronary artery disease.[1,3]

Cutler reported that the prevalence of severe coronary artery disease in patients with PVD is greater than 50%.[3] He concluded that myocardial infarction is the most common cause of early and late postoperative morbidity among patients requiring surgical management of PVD. Risk factors associated with postoperative cardiac events include myocardial infarction six months before surgical therapy, congestive heart failure, ventricular dysrhythmia, previous stroke, and an abnormal resting electrocardiogram (ECG). These risk factors were consistent with those reported by Cooperman and co-workers.[1]

Many investigators have tried to find ways to screen patients with PVD who require a peripheral vascular operation, in an attempt to decrease cardiac morbidity and mortality associated with surgical procedures. These screening methods have included an inventory of risk factors, graded exercise stress testing, and dipyridamole-thallium (D-T) imaging.

Exercise testing using a treadmill has been the "gold standard" for assessing cardiac ischemia in symptomatic and asymptomatic patients. It has been used by many physicians to predict those who will have cardiac complications after a peripheral vascular operation.[2,3]

McCabe and associates reviewed the value of ECG monitoring during treadmill testing for PVD patients.[2] They found that in 44% of 150 patients with a recent history of coronary artery disease, myocardial infarction, or angina, ECG changes developed during testing. They noted that 26% of 125 unselected PVD patients with no documented history of cardiac disease had similar exercise-induced ECG changes develop. They concluded that ECG monitoring with treadmill testing was a good screen for cardiac ischemia in asymptomatic patients with PVD. Similar findings have been reported by Cutler and colleagues.[5]

Eagle and co-workers described the use of D-T imaging to improve preoperative cardiac evaluation in PVD patients before lower extremity revascularization.[4] With this imaging technique, patients are not required to do any exercise. Eagle and colleagues studied 61 patients with preoperative D-T imaging. The presence of thallium Tl 201 redistribution following the intravenous administration of dipyridamole was associated with a 45% increased risk of perioperative complications. They concluded that D-T imaging was useful for stratifying patients at increased risk for cardiac complications who have one or more clinical cardiac symptoms.

McPhail and associates compared exercise stress testing with D-T imaging for predicting perioperative cardiac complications in vascular reconstruction patients.[6] They studied 60 patients who underwent aortic aneurysm or aortoiliac reconstruction with both treadmill exercise or arm ergometry and D-T imaging. Exercise stress testing had a sensitivity of 0.23 with specificity of 0.89, whereas D-T imaging had a sensitivity of 0.86 with specificity of 0.68. They concluded that D-T imaging was a superior screen for cardiac disease in patients with PVD. The low sensitivity of exercise stress testing in these patients was felt to be due to the inability of many patients to generate a sufficient cardiac workload to trigger ischemia.

From the Department of Physical Medicine and Rehabilitation, University of Michigan Medical School (all authors), the Rehabilitation Medicine Service, Veterans Affairs Medical Center (all authors), and the Department of Surgery, St Joseph Mercy Hospital (Dr Lampman), Ann Arbor, Michigan; the Loewenstein Hospital Rehabilitation Centre, Ra'anana (Dr Davidoff), and the Department of Rehabilitation Medicine, Sackler School of Medicine, Tel Aviv University, Ramat Aviv (Dr Davidoff), Israel.

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Reprint requests to Gary Davidoff, MD, Dept of Physical Medicine and Rehabilitation, ID204 University Hospital, Box 0042, Ann Arbor, MI 48109.

ABBREVIATIONS USED IN TEXT

D-T = dipyridamole-thallium
ECG = electrocardiogram
PVD = peripheral vascular disease
RPE = rate of perceived exertion
THR = training heart rate

Cardiovascular Disease in Patients With Amputation for Peripheral Vascular Disease

The prevalence of severe coronary artery disease and associated postoperative cardiac complications in patients with severe PVD is high. Likewise, severe cardiac disease is equally prevalent in vascular amputees admitted for rehabilitation and prosthetic training. Methods of detecting coronary artery disease previously discussed for PVD patients are readily applicable for screening vascular amputees before initiating exercise training and rehabilitation. In addition, ECG monitoring during physical therapy and prosthetic training has been used to evaluate the cardiac status of patients with lower extremity amputation.

Perlman and colleagues reported the use of dynamic ECG (Holter) monitoring during rehabilitation and prosthetic training of 65 elderly patients with unilateral amputation.[7] Cardiac status was evaluated by history, physical examination, chest radiograph, laboratory profile, and resting ECG. A ten-hour ECG monitoring was also performed during routine activities in physical therapy. Various ECG changes during prosthetic training were noted. The most significant and stressful event was single-legged hopping while holding onto parallel bars. Kohn further analyzed Perlman's original cohort and reported that 41 of 58 (70%) had evidence of cardiac disease on admission and that those patients without heart disease progressed more rapidly in their prosthetic training program.[8] These authors concluded that the high prevalence of cardiac disease required modification of the customary training program among elderly amputee patients to safely complete a prosthetic training program.

Kavanaugh and Shephard studied 62 patients admitted for rehabilitation after amputation for PVD.[9] Of the 62, 30 (48%) had a history of myocardial infarction or congestive heart failure, 10 additional patients had diastolic hypertension, and 28 of 60 (47%) had an abnormal resting ECG. In 18 of 27 patients (67%) who underwent exercise stress testing using an arm ergometer, ST segment depression of greater than 1 mm developed. Half of those with exercise-induced ECG changes had previously been asymptomatic and had a normal resting ECG. Exercise-induced ECG changes occurred at moderate workloads (< 50 watts per minute), indicating advanced coronary artery disease. It was concluded that exercise testing could be used to define the limits of safe exercise in this patient population. Similar rates for dynamic ECG abnormalities during exercise stress testing in this population have been documented by Cruts, Finestone, and Davidoff and co-workers.[10-12]

Roth and associates published a report of 31 patients admitted for amputee rehabilitation who were monitored during routine physical therapy sessions for heart rate, blood pressure, and ECG changes.[13] The mean age was 65 years. Of the 31, 17 (55%) had cardiac problems detected by monitoring ECG and vital signs. Four of these patients had no history of cardiac disease. They also found that a history of congestive heart failure, digoxin use, or a delay in admission to rehabilitation of greater than 14 days was closely related to the finding of cardiac problems during monitoring. They concluded that the combination of screening for a history of coronary artery disease and dynamic cardiac monitoring provided the most useful information for detecting cardiac disease in this population.

Van Alsté and colleagues reported the use of symptom-limited exercise testing in patients with lower extremity amputation.[14] They admitted 39 subjects, with a mean age of 67 years, for a prosthetic training program. Of the 39 subjects, 21 (54%) had previous cardiac problems or abnormal resting ECGs. In all, 37 of the patients were studied with graded exercise tests using an arm ergometer. The mean peak workload was 63 watts per minute, and the mean peak heart rate was 124 beats per minute. In 14 of the 37 patients (38%), ST segment depression of more than 1 mm was seen at peak workloads. Five patients showed similar changes at rest. The reasons for terminating the exercise testing included general fatigue (59%), an inability to maintain the rotational speed (23%), and arm and muscle fatigue (18%). None terminated because of chest pain. Similar reasons for terminating exercise stress testing in this patient population have been noted by Finestone and Davidoff and co-workers.[11,12] It was concluded that cardiac problems were common in elderly vascular amputees and that exercise testing was able to detect previously unrecognized cardiac abnormalities. Arm ergometry can also be used to determine safe maximal heart rates for exercise and provide guidelines for the rehabilitation program.

Exercise Training in Patients With Peripheral Vascular Disease or Amputation

Pitetti and associates reported the use of a 15-week aerobic training program in 20 long-term traumatic amputees.[15] Each person was tested using a treadmill stress testing protocol before beginning the exercise training program. Each subject then exercised independently using a Schwinn Air-Dyne ergometer as directed by the training protocol. Only 10 (50%) completed the entire training program. Those who completed the training protocol had a 25% increase in their maximum work capacity. The authors also found a decreased heart rate at submaximal exercise, an increased heart rate at peak exercise, and improved peak oxygen consumption. They concluded that aerobic conditioning improved the cardiovascular fitness and economy of walking in patients with lower extremity amputations.

Previous work from our laboratory resulted in an exercise testing and training program using arm ergometry.[12] This program is used in conjunction with standard rehabilitation for patients with recent vascular amputation who are profoundly deconditioned after complicated perioperative courses. Our protocol is simple to administer and inexpensive. Patients first have a baseline resting ECG. During exercise, a bipolar V_5 lead is used for monitoring arrhythmias and ST segment depression. Patients exercise using an arm crank ergometer in three-minute stages. The resistance begins at 5 watts and is increased by 5-watt increments per stage. Patients exercise for 2 minutes 30 seconds and then crank at zero resistance for 30 seconds so that blood pressure and artifact-free ECG rhythm strips can be recorded. Testing is terminated if a patient's systolic blood pressure drops progressively with increased work, if clinically significant cardiac arrhythmias occur, if the patient loses the capacity to

maintain a steady cranking rate of 50 rpm, and for limb fatigue, angina, or dyspnea.

The training heart rate (THR) for patients is then calculated using Karvonen's formula[16] at a 50% intensity, as given in the following equation:

$$\text{THR} = \text{resting HR} + ([\text{maximal HR} - \text{resting HR}] \times 0.50).$$

While the initial intensity is established at 50%, the goal is to reach an intensity of 70% as patients become better conditioned. Patients initially do interval arm ergometry exercise training using this THR for a total of 15 minutes of aerobic exercise per session. For example, if the THR of 130 beats per minute was associated with a power output of 10 watts per minute for a specific patient, the patient would train as follows: warm-up at no resistance (5 minutes), cycle at 5 watts (5 minutes), cycle at 10 watts (5 minutes), cycle at 5 watts (5 minutes), and a cool-down phase of five minutes consisting of cranking at 0 watts. As the patient's exercise tolerance improves, the duration of cycling at 10 watts would increase until all 15 minutes of aerobic activity could be spent comfortably at 10 watts. At this point the target intensity would be increased to 60% and, if sufficient progress allowed, to 70% using these guidelines. This program is accompanied by morning and afternoon sessions of progressive resistance exercise for major muscle groups of the upper and lower extremities and functional training with a prosthesis when clinically appropriate. This program is conducted five times a week.

So far 25 patients, with a mean age of 63 years, have completed our inpatient program with pretest and discharge work performance assessment. Results showed that heart rate responses were decreased during the early stages of testing, when comparing discharge testing to postoperative findings. The duration of exercise increased from 12.6 minutes to 16.3 minutes ($P < .0004$), and the maximum work output increased from 17.1 watts to 23.5 watts ($P < .0004$). There was no significant morbidity associated with arm ergometry testing or the arm ergometry exercise training and rehabilitation program. We conclude that arm ergometry testing and training is a safe and effective method for improving the upper body muscular strength and efficiency of arm work in patients with recent vascular amputations.

Self-monitoring for Home Exercise Programs

The rate of perceived exertion (RPE) (Table 1) is an instrument for self-monitoring of exercise intensity, usually measured during exercise stress testing.[17] It has been described frequently in the cardiac rehabilitation and exercise literature and is generally felt to be a useful indicator of exercise intensity. This instrument can then be used for self-monitoring in subsequent training.[18,19] Because the aerobic training program commonly used in this patient group is arm ergometry, the RPE could potentially allow patients to indirectly monitor their training intensity without interrupting the exercise routine to measure pulse responses.

Finestone and colleagues studied the association between a patient's heart rate response and RPE using a graded arm ergometry test.[11] The patient population studied included severely deconditioned vascular amputees before and after an inpatient rehabilitation program. They studied 26 men at admission and 11 following completion of the program. Scatter plots and linear regression analyses revealed no statistically significant relationship either at early stages of exercise or at peak work for heart rate or RPE. These results suggest that the RPE should not be used as a substitute for direct pulse measurement in the exercise training of persons with recent vascular amputations.

TABLE 1.—*Borg Rating of Perceived Exertion Scale**

Borg Rating	*Perceived Exertion*
6	
7	Very very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very very hard
20	

*From Borg and Linderholm.[17]

The Influence of Cardiovascular Function on Walking After Vascular Amputation

Waters and co-workers studied the energy costs of ambulation in 70 patients with unilateral amputation (above the knee, below the knee, and Syme's).[20] Patients were tested on a treadmill at a "comfortable walking speed and at fast walking." Noted were higher metabolic costs (peak direct oxygen consumption) in patients with higher anatomic levels of amputation, advanced age, or a history of PVD.

Huang and associates studied the energy costs of ambulation in 25 normal controls, 6 with below-knee, 6 with above-knee, and 4 with bilateral above-knee amputations.[21] The patients were each requested to walk at their most comfortable speed. The investigators found increased energy expenditure in all amputees compared with controls. Those with bilateral above-knee amputations expended three times the energy for walking that normal controls did per meter distance. They concluded that these data need to be considered when prescribing a prosthesis for a person with bilateral above-knee amputations.

In a study of 37 persons with vascular amputations, van Alsté and colleagues reported that all patients with a maximum work capacity of greater than 60 watts per minute on discharge from rehabilitation achieved the ability to walk outdoors with their prosthesis compared with only 38% of patients with a lower work capacity.[14]

Cruts and co-workers studied 39 patients with lower extremity vascular amputations with resting ECG and rowing arm ergometry.[10] All patients had moderate to severe functional aerobic impairment on baseline exercise testing. Rowing arm ergometry was used to determine a safe maximal heart rate for exercise training early in their rehabilitation program. The investigators then correlated the results of baseline functional capacity evaluation with the patients' prosthetic success after rehabilitation. They found that 70% of those patients who achieved a peak work load of greater than 45 watts per minute at admission assessment were able to ambulate without an assistive device at discharge. Of those who failed to achieve a maximal work load of 45 watts per minute at admission, however, 38% were also able to ambulate without walking frames at discharge.

Moore and associates did a retrospective review of 157 patients following major lower extremity amputation for PVD.[22] They examined the association between a history of coronary artery disease and the achievement of household ambulation with a prosthesis. In all, 78% of those with above-knee amputations who failed to achieve household ambulation had a history of coronary artery disease. Only 7% of patients with above-knee amputations who ambulated had a history of coronary disease. Of patients with bilateral amputations who were not ambulatory, 73% had coronary artery disease compared with 20% of bilateral amputee ambulators. There was no difference in the prevalence rates of coronary disease between those with below-knee amputations who achieved or failed to achieve household ambulation. They concluded that the presence of coronary artery disease in elderly persons with above-knee or bilateral amputations because of vascular disease was associated with a decreased likelihood of household ambulation.

Conclusions

Coronary artery disease is prevalent in patients with lower extremity peripheral vascular disease, especially among those who go on to amputation. The use of dipyridamole-thallium imaging in these patients may improve the ability to diagnose asymptomatic coronary artery disease before initiating an exercise program, thereby allowing adequate treatment and preventing complications during rehabilitation. Arm ergometry is a safe and effective exercise alternative for detecting asymptomatic coronary disease in those unable to exercise their lower extremities and can be used to determine safe upper extremity exercise levels in poorly conditioned patients and those with known coronary disease. Arm ergometry testing is also useful for providing prognostic information concerning functional outcome after a rehabilitation program. Exercise testing is therefore indicated in all vascular amputee patients before beginning an exercise training and prosthetic rehabilitation program. Exercise training can safely and inexpensively enhance the functional capacity of amputee patients with PVD. More studies are needed to understand the full effects of exercise testing and training on specific cardiac variables, cardiovascular risk factors, and functional capacity for patients with PVD after amputation.

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REHABILITATION MEDICINE Adding Life to Years

Spinal Cord Injury
Rehabilitation Adds Life to Years

MICHAEL J. DE VIVO, DrPH; J. SCOTT RICHARDS, PhD; SAMUEL L. STOVER, MD; *and* BETTE K. GO, *Birmingham, Alabama*

The National Spinal Cord Injury Statistical Center data base contains information collected prospectively on 13,763 persons injured since 1973 and treated at model systems of care throughout the United States. These data clearly demonstrate improved neurologic status and independent function in activities of daily living following acute care and rehabilitation for most persons with spinal cord injuries. Decreased lengths of initial and subsequent hospital stays and increased survival rates are also documented. Most persons are discharged to a private residence in the community and remain there. Many complete their educations and return to gainful employment after injury. Spinal cord injury has only a short-term effect on marriage and divorce rates, which appears to dissipate within a few years after injury. Overall, these figures demonstrate the dramatic improvements in length and quality of life achieved by most persons with spinal cord injuries during the past two decades.

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In the early 1970s, the US Department of Health, Education, and Welfare began funding a national network of model regional spinal cord injury (SCI) systems of care based on the concept of an organized continuum of services beginning with primary prevention activities and including emergency medical services, acute care, multidisciplinary rehabilitation, community reintegration, and long-term follow-up. Today, 13 of these systems of care are funded by the National Institute on Disability and Rehabilitation Research within the US Department of Education. From its modest beginnings, the program has evolved to include both individual intrasystem and collaborative research activities, as well as the development of a standardized data base presently housed at the National Spinal Cord Injury Statistical Center (NSCISC).

Information from the NSCISC data base on demographics and medical, vocational, and economic outcomes for persons injured from 1973 to 1985 was published in 1986.[1(pp13-60)] This report updates some of the findings published in that book, which are now more than five years old, and supplements those findings with a review of pertinent literature.

Methods

Since 1973, information on acute care, rehabilitation, and annual follow-up has been collected prospectively on 13,763 persons treated at model systems located throughout the country. This information is submitted on standardized forms in accordance with a detailed set of instructions that is reviewed and revised periodically to enhance both validity and reliability. All data are subjected to several quality control measures, including visual inspection for face validity and computer cross-checking of variables for internal consistency with current and prior information submitted for each patient. No data are used for analysis until they pass quality control.

Current eligibility criteria for a patient to be included in the data base are as follows:

- SCI due to trauma;
- Admission to a model system of care within 60 days of injury (within 365 days of injury for persons injured before October 1986);
- Place of injury and residence within the geographic catchment area of the model system;
- Clinically discernible degree of spinal cord neurologic impairment on admission (spinal column fractures without neurologic deficit are excluded);
- Continual hospitalization from injury to model system admission, except for brief periods no longer than normally accepted as a therapeutic leave of absence;
- Discharge from the model system as either neurologically recovered, completed rehabilitation, or died; and
- Signed informed consent.

Some of the following analyses include all patients in the data base, and others use samples appropriate to the question under consideration. For example, to avoid possible selection bias and confounding by treatment practices at other facilities, some analyses are restricted to persons admitted to the model system within 24 hours of injury. Therefore, the exact number of patients used is identified for each analysis.

Results

Demographics

The mean age for all patients studied is 30.5 years (standard deviation, 14.9). The median age is 26 years; the most common age is 19 years, and 59.3% of patients are between the ages of 16 and 30 years. The effect of age on rehabilitation outcomes for persons with SCI has been documented in detail elsewhere.[2]

Overall, 82.3% of persons enrolled in the NSCISC data base are male. As with most injuries, the incidence rate of

From the Department of Rehabilitation Medicine, Spain Rehabilitation Center, University of Alabama at Birmingham.

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Reprint requests to Michael J. DeVivo, DrPH, 548 Spain Rehabilitation Center, 1717 Sixth Ave S, Birmingham, AL 35233.

ABBREVIATIONS USED IN TEXT

DVR = Department of Vocational Rehabilitation
FIM = functional independence measure
NSCISC = National Spinal Cord Injury Statistical Center
SCI = spinal cord injury

SCI is higher among nonwhites.[3,4] Because there are so many more white persons in the United States, however, most persons who sustain these injuries are white, including 71.1% of persons enrolled in the NSCISC data base.

Motor vehicle crashes are the leading cause of SCI (44.8%), followed by falls (21.7%), acts of violence (16.0%), sports (13.0%), and all other causes (4.5%). Almost all spinal cord injuries due to acts of violence are the result of gunshot wounds (89.6%), and most sports-related spinal cord injuries are due to diving accidents (66.5%).

Neurologic Impairment and Recovery

The neurologic level of injury is defined as the most caudal spinal cord segment that tests normal for both sensory and motor function. Overall, 54.2% of persons enrolled in the NSCISC data base had cervical injuries, 35.3% had thoracic injuries, and 10.5% had lumbosacral injuries. More than 42% of persons enrolled in the data base had injuries at the C-4 (13.0%), C-5 (16.0%), or C-6 (12.9%) levels. The next most common level of injury was T-12 (7.5%). Persons with cervical injuries are classified as having quadriplegia, and persons with lower level lesions are classified as having paraplegia. The percentage of cervical injuries is substantially higher among persons enrolled in the NSCISC data base than has been observed in population-based studies[3,5]; thus, it appears that more severely injured persons are disproportionately sent to model systems for treatment whereas less severely injured persons are disproportionately treated at other facilities.

Another important measure of injury severity is the degree of preserved neurologic function below the lesion level. For persons enrolled in the NSCISC data base, the degree of preserved neurologic function was assessed using Frankel's classification system.[6] The five classification categories in this system are as follows:

- **A,** Neurologically complete: no preservation of any motor or sensory function below the zone of partial preservation;
- **B,** Preserved sensation only: preservation of any demonstrable, reproducible sensation excluding phantom sensation below the zone of partial preservation;
- **C,** Preserved motor (nonfunctional): preservation of voluntary motor function that is minimal and performs no useful purpose; minimal is defined as preserved voluntary motor ability below the level of injury where the majority of key muscles test less than grade 3;
- **D,** Preserved motor (functional): preservation of functionally useful voluntary motor function in which the majority of key muscles below the level of injury test at least grade 3; and
- **E,** Complete recovery: complete return of all motor and sensory function, although reflexes may still be abnormal.

For our purposes, the zone of partial preservation is defined as three or fewer neurologic segments at the point of damage to the spinal cord, where there is frequently some preservation of motor or sensory function.

TABLE 1.—*Change in Degree of Preserved Neurologic Function (Frankel Grade) Between Injury and Discharge From Rehabilitation (n = 4,934)*

	Frankel Grade Changes, %				
Frankel Grade	*Percent at Injury*	*Improved*	*No Change*	*Declined*	*Percent at Discharge*
Complete (A)	51.9	10.3	89.7	...	47.4
Preserved sensation (B)	13.1	45.2	50.3	4.5	9.3
Motor, nonfunctional (C)	13.1	55.9	41.5	2.6	9.0
Motor, functional (D)	21.9	7.3	90.7	2.0	32.3
Recovery (E)	...	...	...	...	2.0

To assess the degree of neurologic recovery, only persons admitted to the model system within 24 hours of injury for whom complete neurologic data were available at both admission and discharge were used (n = 4,934). Initially, 51.9% of lesions among these persons were neurologically complete, 13.1% were Frankel grade B, 13.1% were Frankel grade C, and 21.9% were Frankel grade D (Table 1). Only 10.3% of persons with complete injuries had neurologic improvement sufficient to alter the Frankel grade by the date of discharge. However, 45.2% of persons with Frankel grade B injuries and 55.9% of persons with Frankel grade C injuries had substantial neurologic improvement of at least one Frankel grade by the date of discharge. Although most persons with Frankel grade D injuries on admission continued to have a measurable degree of impairment at discharge, most showed some improvement, and 7.3% had complete neurologic recovery. Moreover, some persons continued to improve neurologically for as long as 18 months after discharge. Continued neurologic improvement beyond 18 months after injury is relatively rare.

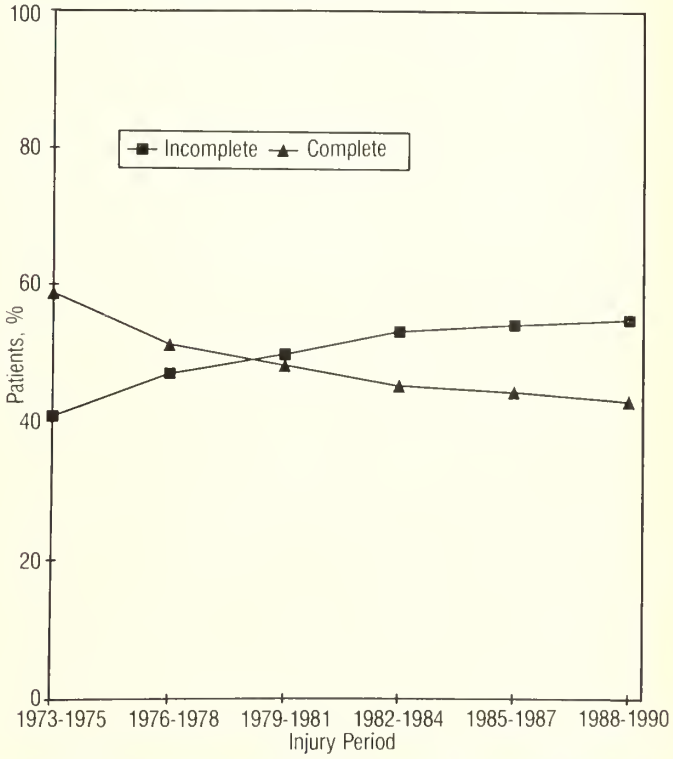

Figure 1.—Neurologic extent of injury at discharge is compared by injury period for all persons enrolled in the national spinal cord injury data base (n = 13,763).

TABLE 2.—*Mean Gain in Total Functional Independence Measure Score Between Admission to and Discharge From Rehabilitation by Neurologic Level and Degree of Injury Completeness (n=751)*

	Total Functional Independence Measure Score			
Time	Incomplete Paraplegia, n=179	Complete Paraplegia, n=211	Incomplete Quadriplegia, n=242	Complete Quadriplegia, n=119
Admission to rehabilitation	73	68	59	47
Discharge from rehabilitation...	110	104	93	62
Gain during rehabilitation	37	36	34	15

The percentage of all persons enrolled in the NSCISC data base with neurologically incomplete lesions at discharge is depicted by injury year in Figure 1. The proportion of persons with neurologically incomplete lesions at discharge increased from 40.8% during 1973-1975 to 55.2% during 1988-1990. This increase in the percentage of neurologically incomplete lesions is undoubtedly the result of secondary prevention activities, such as the use of seat belts to reduce injury severity, improved emergency medical services at the scene of accidents to prevent initially incomplete injuries from becoming complete, and improved methods of medical and surgical management during acute care and rehabilitation. In fact, these figures probably underestimate the actual trend because of the bias in recent years toward disproportionate referral of severely injured persons to model system facilities.

Functional Enhancement

Since October 1988, the functional capability of persons enrolled in the NSCISC data base has been assessed by the functional independence measure (FIM) that is recorded at the time of admission to rehabilitation and at discharge from rehabilitation. The FIM was introduced in 1986 by the Task Force to Develop a Uniform Data System for Medical Rehabilitation and is currently in use at many facilities throughout the country.[7] It is an 18-item, 7-level ordinal scale, with 18 being the lowest possible score and 126 the highest, representing the most independent level of function. Items include feeding, grooming, bathing, dressing upper and lower body, toileting, bladder and bowel control, transfer to bed or chair, toilet, tub or shower, locomotion, stair climbing, communication (comprehension and expression), and social cognition (social interaction, problem solving, and memory).

So far, these data have been collected on 751 persons enrolled in the data base; the results appear in Table 2. The mean total FIM score at rehabilitation admission ranged from 73 for persons with neurologically incomplete paraplegia to 47 for those with neurologically complete quadriplegia. Mean total FIM scores at discharge ranged from 110 to 62 for the same neurologic categories. Mean total FIM score gain was essentially the same for all persons (34 to 37 units) except for those with neurologically complete quadriplegia, who had an average gain of 15 units during rehabilitation. With appropriate outpatient therapy, continued improvement may occur following discharge.

Length of Hospital Stay

The total length of hospital stay for acute care and rehabilitation for persons enrolled in the NSCISC data base appears in Figure 2. Once again, only persons admitted to the model system within 24 hours of injury were included in this analysis to avoid confounding by treatment practices at other facilities. As can be seen, the mean length of hospital stay has decreased substantially since the program began. In 1974, the mean length of hospital stay was 149.6 days for persons with quadriplegia and 122.3 days for persons with paraplegia. By 1989 (the most recent year for which complete data are available), the mean length of hospital stay had decreased to 92.4 days and 74.9 days for persons with quadriplegia and paraplegia, respectively.

Place of Residence

Among persons who completed rehabilitation (n = 13,330), 94.1% were discharged to a private residence within the community, 4.0% were discharged to a nursing home, 1.5% were discharged to another hospital, and 0.4% were discharged to another destination. Moreover, among 1,366 persons who were being followed ten years after injury, 98.0% still resided in private residences within the community.

Level of Education

Of patients enrolled in the NSCISC data base, 55.6% had at least a high school education. Of those admitted between the ages of 18 and 21 years, 67% had at least a high school education, somewhat less than the nationwide norm of 78%.[8(p150)] Approximately 11.7% of the sample had an 8th-grade education or below. These figures represent only the number of grades of school completed; they do not necessarily reflect the level of academic achievement. Overall, 51.2% of those with a 9th- to 11th-grade education successfully completed their high school education within the first five years following injury. Of those with a high school education at the time of injury, 11.6% achieved a higher academic degree within the first five years following injury. An unknown additional percentage may have been pursuing post-secondary education, but our figures do not reflect those persons. Although it would be difficult to determine the percentage of persons with these demographic and socioeconomic characteristics who would be expected to finish high

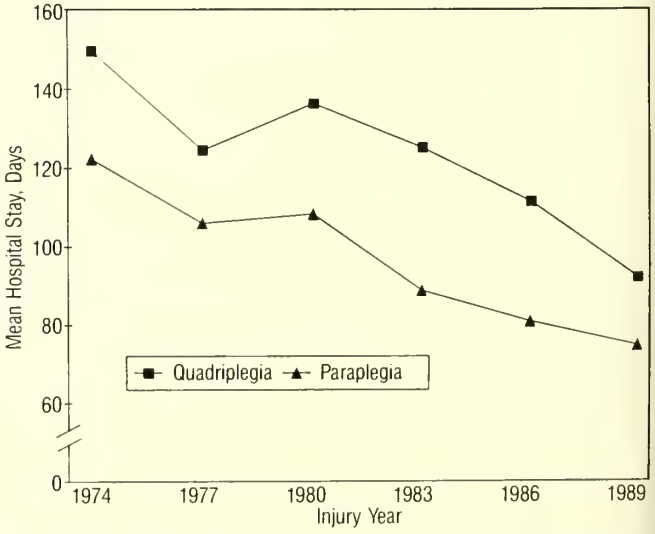

Figure 2.—Mean days of hospital stay for acute care and rehabilitation are compared by injury year and neurologic level of injury for persons admitted within 24 hours of injury to a model system facility (n=4,889).

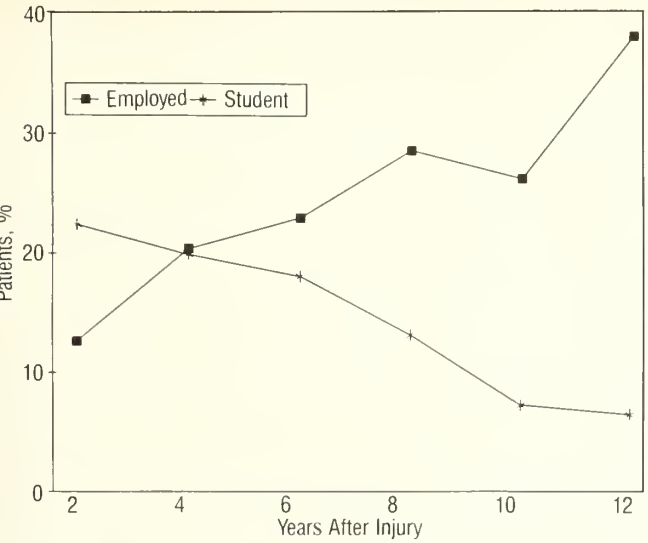

Figure 3.—The percentage of persons with spinal cord injuries between 16 and 59 years of age who are either employed in the competitive labor market or in school each year after injury is shown (n = 6,862).

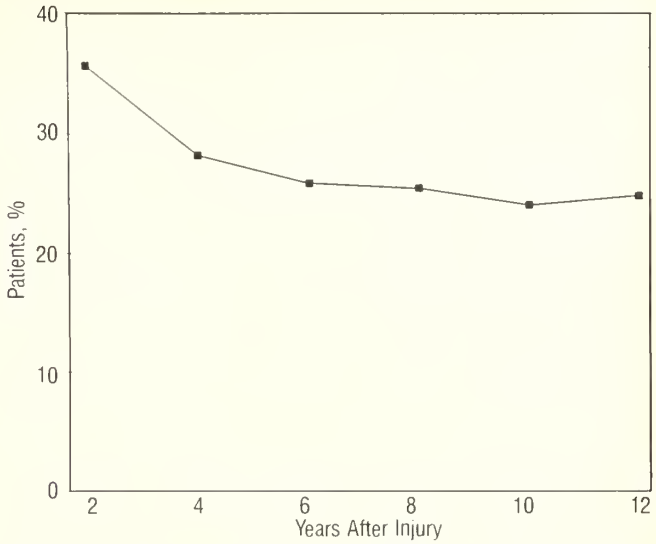

Figure 4.—The percentage of all persons enrolled in the national spinal cord injury data base who are readmitted to a hospital each year after injury is shown.

school or postsecondary degrees or both in this time span, it is clear that many persons with SCI successfully further their education after injury.

Employment

The percentage of persons with SCI who are either employed in the competitive labor market or in school are compared by postinjury year in Figure 3. Only persons between 16 and 59 years of age with known employment status were included in this analysis (n = 6,862). The percentage of employed persons increased from 12.6% 2 years after injury to 38.3% 12 years after injury. Persons who are reemployed shortly after injury virtually always return to the same job with the same employer, whereas those whose reentry into the labor market is delayed usually obtain a different type of job with a different employer, often after appropriate retraining. At the time of injury, 63.7% of these persons were employed and 14.7% were students. Significant predictors of postinjury employment include younger age, male sex, being white, having a higher educational level, being highly motivated, having higher functional ability scores, and being employed before the injury.[9]

Client Status

Only 6.5% of the NSCISC sample were Department of Vocational Rehabilitation (DVR) clients at the time of admission, but this proportion had increased to 37.9% by discharge. There was a steady decline in the percentage of persons with SCI who remained DVR clients over time. By 13 years after injury, only 8.2% were still DVR clients. These data mirror the data presented elsewhere on educational and occupational status. It appears that many persons with SCI seek further education after injury and, with the help of DVR, are able over time to return to some form of gainful employment.

Marital Status

Of persons with SCI who were enrolled in the data base, 53.4% were single at the time of injury, a fact that is not surprising given the young age at which most injuries occur. Most (88%) of those single at injury remained so five years after injury, however, whereas the expected percentage of those remaining single for an age-sex-matched uninjured control group would be 65.3%. Similarly, in the NSCISC sample, the attrition rate of intact marriages at the time of injury is slightly higher than that of an age-sex-matched uninjured control group. Of 1,001 persons with SCI married at the time of injury, 80.7% were still married five years later; the expected percentage remaining married for persons without SCI would be 88.8%. Visual examination of the data suggests that the risk for divorce assumes an inverted U-shaped function during the first five years after injury: little difference between the divorce rates of SCI and matched uninjured groups during the first year after injury, a relatively greater risk for divorce among persons with SCI during the second and third years, and close to the expected rate of divorce during the fourth and fifth years. Although further follow-up is needed, these figures imply that, after an initial period of high risk, divorce rates for persons with SCI may return to normal. Significant risk factors for divorce include young age, being female, being black, having no children, having previous marriages that ended in divorce, and being nonambulatory.[10]

Postdischarge Readmission to Hospital

The percentage of persons with SCI who are readmitted to a hospital each year after injury appears in Figure 4. About a third of all persons with SCI are readmitted to a hospital at least briefly during the rest of the first postinjury year following rehabilitation discharge. During the second year after injury, 35.7% of persons with SCI are rehospitalized. This percentage declines steadily thereafter, however, such that by the 12th postinjury year, only 25% are readmitted. Among persons who are readmitted to a hospital, many have more than one admission, and the average length of stay for all hospital stays during the year is approximately 25 days. Interestingly, there are considerably fewer readmissions and shorter lengths of stay today than there were in the early 1970s.[11] For example, the length of stay per readmission during the second postinjury year has decreased from 15.5 days before 1980 to 11.7 days in 1988.

Survival

The overall 16-year cumulative survival for persons with SCI enrolled in the NSCISC data base is 76.9%. In fact, during the first 12 years after injury, the cumulative survival has increased to slightly more than 88% of what would be expected in the absence of injury.[12] Younger persons, those with paraplegia, and those with neurologically incomplete injuries have even better relative survival rates.[12,13]

Years ago, the leading cause of death for persons with SCI was renal failure. Today, with improved methods of prevention and management, deaths due to renal failure during the first 12 years after injury are uncommon.[14,15] Instead, causes of death with the highest excess mortality are pneumonia; pulmonary embolism; and septicemia due to pressure sores or respiratory or urinary tract infections.[14,15] In fact, life expectancies would approach (but not yet equal) normal if these three causes of death were eliminated.

Discussion

Developing and maintaining a national collaborative SCI data set has allowed us to track changes over time in the basic demographic, neurologic, and medical characteristics of persons with SCI and to document changes in rehabilitation outcomes. Prospects for surviving SCI appear to be improving, and more persons who receive such injuries are left with neurologically incomplete (hence more remaining functional ability) rather than complete injuries. Improvements in post-acute care have resulted in a substantial reduction in morbidity and mortality due to renal complications. Our data further suggest that the next focus for improving survival rates should be in the areas of pulmonary function and septicemia. Persons with SCI frequently return to school to further their education, and an increasing number are also able to return to competitive employment over time. The fact that some persons with SCI do not return to work is likely a reflection of a number of factors, such as functional limitations, societal and architectural barriers, and financial disincentives.

Increasingly, questions are being raised about quality of life and aging with an SCI.[16] The primary research focus in the past has been on acute care and rehabilitation, but, increasingly, researchers are studying the short- and long-term outcomes following rehabilitation for this group of persons and their families. Survival is important, but the resulting quality of life is even more important.

For the most part, the developing picture indicates that a high quality of life can be achieved. For example, earlier views that depression was inevitable and often prolonged and severe are being replaced by empiric data suggesting this is not necessarily so.[17,18] Several interventions are now available to improve the mechanics of male sexual functioning and increase the possibilities for fathering children. Access to the world outside the home has been augmented by legislation mandating the removal of architectural barriers. Persons with SCI are therefore more able to return to school and work and to become involved in the social and cultural mainstream.

Adjusting to SCI is an ongoing process, and higher-than-expected divorce rates for the first few years after injury suggest that a toll may be exacted for some persons. A return to or initiation of drug or alcohol abuse or both is also a problem for some persons.[19] Other findings suggest that persons with SCI do best when they have an effective social support system.[20] These findings together suggest that more research is needed on the effects of SCI on care givers and that follow-up contact and social support services may be needed along with medical follow-up.

Persons with SCI, along with other persons with disabilities, are becoming increasingly effective legislative advocates for themselves. The recent passage of the Americans With Disabilities Act is a case in point.[21] The focus of this legislation is on eliminating architectural and attitudinal barriers to full participation in the mainstream of society. In a sense, the message from persons with disabilities is that they are only as handicapped as we make them. If we give them the tools, they will do the rest. Facilitating the feeling of and possibility for control and self-direction is one of the next great challenges for rehabilitation.

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Pregnancy Following Spinal Cord Injury

LELAND L. CROSS, MD, MPH; JAY M. MEYTHALER, JD, MD; STEPHEN M. TUEL, MS, MD; *and*
AUDREY L. CROSS, RN, *Charlottesville, Virginia*

Each year about 2,000 women of childbearing age in the United States have a spinal cord injury. Only a few mostly anecdotal reports describe pregnancy after such an injury. In a retrospective study of 16 women with a spinal cord injury, half of whom have a complete injury and about half quadriplegia, 25 pregnancies occurred, with 21 carried to full term. The women delayed pregnancy an average of 6.5 years after their injury, with an average age at first pregnancy of 26.8 years. Cesarean section was necessary in 4 patients because of inadequate progress of labor. In 5 deliveries an episiotomy and local anesthesia were required, 7 required epidural anesthesia, including all cesarean sections, and 10 did not require anesthesia. Several complications have been identified in the antepartum, intrapartum, and postpartum periods including autonomic hyperreflexia, premature labor, pressure sores, urinary tract infections, abnormal presentation, and failure to progress. Ultrasonography and amniocentesis were used selectively. Women with spinal cord injuries can have healthy children, although there are significant risks and these women have special needs.

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The medical literature pertaining to pregnant women who have had a spinal cord injury (SCI) is largely anecdotal. In 1963 Robertson and Guttman reported on 28 pregnancies in women with SCI.[1] Since that report, the problems of pregnancy, labor, delivery, and the postpartum period have remained relatively unchanged. Our understanding, technology, and the management of the problems of women who have had SCI have improved considerably, however. For example, urinary tract management has progressed from the introduction of the Foley catheter in the 1940s to various other options, including the suprapubic catheter and ileal conduit (or loop). Although urinary tract infections persist, bladder management has improved, and there are newer antibiotics. A recent review article by Stover and co-workers covers many aspects of urologic care,[2] but there is no current publication specifically addressing urinary tract infections in pregnant SCI women.

Autonomic hyperreflexia (autonomic dysreflexia) was described in part as early as 1890 by Bowlby and later by Head and Riddock in 1917.[3] The complete syndrome was described in 1947 by Guttman and Whitteridge.[4] Erickson and Kewalramani have provided an excellent review and understanding of autonomic hyperreflexia.[5,6] This condition may occur in patients with injury at the T-10 level or above, especially above T-6.[7] The syndrome is initiated by stimuli, usually below the level of the SCI. The characteristic symptoms and signs are excessive sweating, splotchy rash, pilomotor erection (usually above the level of injury), facial flush, congestion of nasal passages, paroxysmal hypertension, bradycardia, and a severe throbbing headache.[5] The cases of two patients who have experienced intraventricular bleeding, one fatal, have been reported.[8] These complications have been reported in pregnant women in whom severe hypertension developed without recognition or adequate treatment of autonomic hyperreflexia.[8,9] Many authors recommend epidural anesthesia for pregnant women with SCI to control autonomic dysreflexia during labor and delivery.[10-13] Cesarean section requires a level of anesthesia above T-10, which is also adequate for autonomic hyperreflexia control. Spinal anesthesia for cesarean section is as effective for preventing or terminating autonomic hyperreflexia but has administration problems over longer labor periods.

Aside from the control of autonomic hyperreflexia, analgesic and anesthetic requirements for labor and delivery in women with SCI have only recently received adequate attention. Definitions of terms must be thoroughly understood. Tetraplegia or quadriplegia can be used interchangeably, but paraplegia must be reserved for patients with spinal

TABLE 1.—*Summary of Outcome of 25 Pregnancies in 16 Women With Spinal Cord Injury (SCI)*

Outcome	*Number*
Babies	22
Premature	1
Abortions	3
Induced	2
Spontaneous	1
Fetal birth weight, grams (lb)	
1,431 (3+)	1
2,268 to 2,719 (5 to 6)	4
2,720 to 3,174 (6 to 7)	4
3,175 to 3,629 (7 to 8)	11
3,630 to 4,082 (8 to 9)	2
Apgar scores	
1 at 1 min; 7 at 5 min; 9 at 10 min	1*
7 at 1 min; 8 or more at 5 min	5
9 or 10 at 1 min	16

*The mother has C-2 Frankel classification D SCI and is ventilator-dependent at night for sleep apnea. She was admitted through the emergency department with history of a 2-hour labor with 1 foot presenting. Delivery of a double-footling breech presentation was accomplished without anesthesia.

From the Department of Physical Medicine and Rehabilitation, University of Virginia Health Sciences Center, Charlottesville, Virginia.

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Reprint requests to Leland L. Cross, MD, MPH, Department of Physical Medicine and Rehabilitation, University of Virginia Health Sciences Center, Charlottesville, VA 22908

TABLE 2.—*Cause and Classification of Spinal Cord Injury and Patient Age*

Identification Code	Spinal Cord Injury: Cause	Neurologic Level	Frankel Classification*	Age at Injury, yr
A	MVA	C-2	D	21
B	Gunshot wound	C-3	D	23
C	Skydiving	C-5	B	24
D	MVA	C-5	D	18
E	Diving	C-6	B	18
F	MVA	C-6	D	16
G	MVA	C-6	D	15
H	MVA	T-2	A	16
I	MVA	T-4	A	18
J	MVA	T-8	A	25
K	MVA	T-10	B	16
L	MVA	T-10	A	17
M	MVA	T-10	A	20
N	MVA	T-10	A	27
O	MVA	T-12	A	22
P	Fall from horse	T-12	A	19

MVA = motor vehicle accident

*A: complete loss of motor and sensory function below the level of injury; B: partially preserved sensation below the level of injury; D: useful motor function below the level of injury.

cord dysfunction below T-1—that is, no upper extremity involvement. Patients' sensations during labor and delivery are related to the level of injury and the completeness of the SCI. The highest entry level of sensation into the spinal cord from uterine contraction is T-10.[7] Cervical dilatation sensation is a level or two below this. Sensation in the vagina, perineum, and surrounding tissues send impulses through lumbosacral root afferents. Patients with complete T-12 level dysfunction do feel uterine contractions as painful or uncomfortable. Patients with incomplete SCI usually have sensation, although it may be partial. Definitions of complete and incomplete SCI have been established by Frankel and associates in 1969 and will be discussed later.[14]

Premature labor may occur with increased frequency in SCI women, especially in patients with upper dorsal and cervical SCI.[1,15,16] Early hospital admission or careful monitoring of the cervix for evidence of effacement, dilatation, or progression of labor is important to assure full-term pregnancies.

Fetal age determination using ultrasonography should be done during the 18th to the 22nd week of gestation.[17] Amniocentesis has been used to provide evidence of pulmonary maturation through the lecithin:sphingomyelin ratio. This value can provide an indication for the safe timing of medical or obstetric interventions and allow for additional maturation if indicated. The use of tocolytic agents may postpone premature labor if needed, providing there are no contraindications for their use.

TABLE 3.—*Time Span From Spinal Cord Injury to Delivery*

Date of Injury	Level of Injury	Frankel Classification*	Date of Delivery	Years From Injury to Delivery	Age at Delivery
1950s	T-10	A	1956	6	23
1972	T-4	A	1983,1985	11	29
1972	C-3	D	1978	6	29
1973	C-5	B	1979,† 1982,1985	9	33
1974	T-10	A	1977,1979	3	30
1974	T-12	A	1983	9	31
1974	T-10	B	1983,1985,1986	9	25
1976	C-6	D	1980,1982	4	19
1976	T-10	A	1983	7	19
1978	T-8	A	1987	9	34
			Average	7.1	26.7
1982	C-6	B	1988,‡ 1989	7	25
1983	T-12	A	1984	1	20
1983	C-5	D	1988,1989	5	23
1984	C-6	D	1989	5	21
1984	T-2	A	1990†	6	22
1984	C-2	D	1989	5	26
			Average	4.8	22.8

*See Table 2 †Spontaneous abortion ‡Induced abortion.

Patients and Methods

The Virginia Regional Spinal Cord Injury System identified 16 women with SCI. A five-page questionnaire was used to gather the data by personal or telephone interview. Supplemental information was obtained from several of the patients' hospital records. We used the Frankel classification to interpret our data[14]:

Frankel classification A refers to a complete loss of motor and sensory function below the level of injury. Classification B refers to partially preserved sensation below the level of injury. Classification C refers to preserved, but not useful, motor function below the level of injury. Classification D refers to useful preserved motor function below the level of injury. Classification E refers to normal motor and sensory function but with possibly abnormal reflexes. The American Spinal Injury Association has defined the level of injury as "the lowest normal neurological segment with both motor and sensory function."[18]

Results

There were 25 pregnancies in 16 women, resulting in 22 babies and 3 abortions, of which 2 were induced and 1 was spontaneous (Table 1).

The causes of the spinal injuries included 12 motor vehicle accidents (1 involving a motorcycle) and 1 each due to a fall, skydiving, diving, and gunshot wound (Table 2).

Seven patients had a cervical level of injury, and nine had a thoracic level (Table 2). All the cervical injuries were incomplete SCI. The two patients, one with C-5 level and the other with C-6 level SCI, were Frankel class B (sensory incomplete). All others were Frankel class D (motor useful). The nine thoracic SCI patients were complete with one exception, a patient with T-10 Frankel class B.

The decades of delivery included one in the 1950s, a patient with a T-10 complete injury who had her baby after a premature precipitated labor at home, unattended. Her only awareness of labor and impending delivery was a bloody show. The amniotic sac was ruptured at delivery but still covered the baby. Both were taken to the hospital and ultimately both did well. There were no deliveries in the 1960s. Two babies were born in the 1970s, 19 in the 1980s, and so far only one in the 1990s (Table 3).

For SCI women who were injured in the 1970s, the average age at delivery was 28 years, and for the mothers who were injured in the 1980s, the average age at delivery was 22.8 years. The 1970 group waited 7.3 years after SCI, and the 1980 group waited 4.8 years to deliver their first baby.

Urinary tract management in this group of patients' pregnancies reflects almost the entire spectrum of methods (Tables 4 through 7). Normal voiding, six pregnancies; Credé's method, seven pregnancies; intermittent catheterization, six pregnancies; Foley catheter, three pregnancies; suprapubic catheter, two pregnancies; ileal conduit, one pregnancy.

TABLE 4.—*Urinary Tract Management During Pregnancy in Patients With Spinal Card Injury With Normal Vaiding Pattern*

Identificotion Code	Level of Injury	Fronkel Clossificotion*	Infections Per Pregnoncy, No.	Antibiotics Used
D.....	C-5	D	0	No
D.....	C-5	D	2	Yes†
F.....	C-5	B	0	Yes‡
K.....	T-10	B	0	Yes‡
K.....	T-10	B	1	Yes‡
K.....	T-10	B	0	No

*D: motor function preserved below the level of injury; B: sensation partially preserved below the level of injury.
†Antibiotics given for symptomatic infections only
‡Nitrofurantoin (Macrodantin), 50 mg twice a day, given for prophylaxis.

TABLE 5.—*Urinary Tract Management During Pregnancy in Patients With Spinal Card Injury Using Credé's Methad far Bladder Emptying*

Identificotion Code	Level of Injury	Fronkel Clossificotion*	Infections Per Pregnoncy, No.	Antibiotics Used
C.....	C-5	B	0	Yes†
C.....	C-5	B	0	Yes†
C.....	C-5	B	0	Yes†
L.....	T-10	A	0	No
N.....	T-10	A	0	No
N.....	T-10	A	1	Yes†
O.....	T-12	A	0	No

*B: sensation partially preserved below the level of injury; A: complete loss of motor and sensory function below the level of injury.
†Nitrofurantoin (Macrodantin), 50 mg twice a day, given for prophylaxis.

Symptomatic infections occurred in 100% of patients during pregnancy (fever, chills, and so forth) in the patients using Foley or suprapubic catheters or ileal conduits for bladder management. Only 5 of 19 patients (26%) using the Credé's method, having normal voiding, or doing intermittent catheterization had urinary tract infections that were symptomatic during the pregnancy, although 5 of 12 patients (42%) had infections during pregnancy. One patient with a Foley catheter was admitted to hospital with urinary sepsis requiring intravenous antibiotic treatment. No prophylactic antibiotics were used in the retention cathcter and ileal conduit group.

Only one patient reportcd significant premature labor. Two others were given terbutaline sulfate (10 days) or ritodrine (3 days) for tocolysis and without adverse effect and had full-term babies.

The use of ultrasonography was found to be increasing since its introduction in the 1960s. In the 1970s, 1 of 4 (25%) pregnancies was assessed in this manner versus 14 of 16 (88%) in the 1980s and 1 of 1 (100%) in the 1990s. Amniocentesis is available primarily in major medical centers. Only two (9%) of these patients had this procedure. In nine medical inductions, oxytocin was used; four of these were without amniocentesis or ultrasonography before the induction.

To control autonomic hyperreflexia during labor and cesarean section, four patients in five deliveries received epidural anesthesia (Table 8). One patient without autonomic hyperreflexia chose to have epidural anesthesia for both deliveries. Two patients, both cervical SCI and Frankel classification D, went untreated for autonomic hyperreflexia during labor and delivery. One of these two, however, did receive a local anesthetic for episiotomy and repair. For episiotomy and repair, only 5 of 15 deliveries required local anesthesia. Epidural anesthesia was used for all seven patients having cesarean sections. One patient required the epidural catheter to remain in place for five days postpartum to control autonomic hyperreflexia associated with pains after delivery.

Various medications were used during pregnancy. One patient took oxybutynin chloride (Ditropan) throughout two pregnancies; imipramine hydrochloride, 50 mg at bedtime, was taken by one patient throughout two pregnancies; diazepam, 2.5 mg, was taken once daily throughout two pregnancies. Nitrofurantoin, 50 mg twice a day, was given to five patients throughout their eight pregnancies. Other medications were discontinued early or given only briefly, such as those given for urinary tract infections. Vitamins and minerals were often given.

All mothers who chose to nurse their infants were able to do so. One reported an increase in spasms and spasticity during nursing.

Numerous complications associated with pregnancies were noted in this study of SCI women. These are summarized in Table 9.

Discussion

From the literature and our experiencc, it is apparent that spinal cord-injured women can give birth to healthy infants. Although temporarily altered in some women, menses usually return to normal six to nine months after injury, and subsequent fertility is not altered.[7,19] Contraception is practiced using a variety of methods with varied success as in able-bodied women.[16] The concerns about the use of oral contraceptives in women with SCI are similar to those in able-bodied women. The use of oral contraceptives has increased risks for those who smoke, are older than 35 years, and who have a history of thromboembolism. Spinal cord-injured women are at a greater risk for thrombophlebitis and pulmonary embolism than the able-bodied population even without pregnancy. Even so, information from unpublished reports indicates that more than 50% of spinal cord-injured women use oral contraceptives after the injury.

Once pregnancy has occurred, there may be concerns for women who require medications for spasticity. The medications most commonly used are baclofen and diazepam. A sudden withdrawal of baclofen can cause seizures, so this medication should be tapcred. Anticonvulsant agents such as phenytoin or carbamazepine should also be tapered rather than suddenly discontinued. Diazepam has known addictive properties, and infants have experienced withdrawal after birth. Diazepam is associated with an increased incidence of

TABLE 6.—*Urinary Tract Management During Pregnancy in Patients With Spinal Card Injury Using Intermittent Catheterizatian far Bladder Emptying*

Identificotion Code	Level of Injury	Fronkel Clossificotion*	Infections Per Pregnoncy, No.	Antibiotics Used
G.....	C-6	D	1	Yes†
G.....	C-6	D	0	No
H.....	T-2	A	0	Yes‡
J.....	T-8	A	0	No
P.....	T-12	A	2	Yes†
A.....	C-2	D	0	Yes§

*D: motor function preserved below the level of injury; A: complete loss of motor and sensory function below the level of injury.
†Antibiotics given for symptomatic infections only.
‡Norfloxacin, 400 mg a day, given for prophylaxis.
§Nitrofurantoin (Macrodantin), 50 mg twice a day, given for prophylaxis.

TABLE 7.—*Method of Bladder Management During Pregnancy in Patients With Spinal Cord Injury and Use of Antibiotics*

Identification Code	Level of Injury	Bladder Emptying Method	Frankel Classification*	Infections Per Pregnancy, No.	Antibiotics Used†
B.....	C-3	Urethral retention catheter	D	≥1	Yes
E.....	C-6	Urethral retention catheter	B	≥1	Yes
E.....	C-6	Urethral retention catheter	B	≥1	Yes
I.....	T-4	Suprapubic catheter	A	≥1	Yes
I.....	T-4	Suprapubic catheter	A	≥1	Yes
M....	T-10	Ileal conduit	A	≥1	Yes

*See Table 2.
†None of these patients were taking prophylactic antibiotics.

cleft palate. In studies of baclofen use in rats, there was an increased incidence of omphaloceles and failure in the development of some ossification sites. The use of baclofen in humans during pregnancy has not been reported. Many other drugs, including antibiotics, present an increased risk to a fetus. Current drug information must be reviewed to make certain a drug's use is warranted during pregnancy. The same is true of irradiation—for injuries, pelvimetry, or intravenous pyelography. Alcohol use and smoking are well known to cause substantial adverse effects on a fetus. These risks are not known to be greater in pregnant SCI women, but women should be counseled against their use.

Urologic status should be addressed and, if needed, urologic consultation obtained. As gestation approaches 18 weeks, an ultrasonogram should be done to determine fetal age. As pregnancy reaches seven months, patients need instruction on how to monitor uterine contractions because they may not perceive painful contractions at the start of labor (T-10 and above complete SCI). Regular monitoring of the cervix by the physician for the state of effacement and amount of dilatation is needed, perhaps as much as twice a week. Developing a contingency plan regarding proximity to the delivery location, familiarity with the anesthesiologist, and anesthesia to be used is essential. If the patient has had autonomic hyperreflexia in the past, the pregnancy must be considered high risk and plans for delivery in a tertiary medical center are recommended. Obstetric hospital personnel must be aware of its occurrence, how to differentiate it from preeclampsia, and alternative treatment options.

TABLE 8.—*Incidence of Autonomic Hyperreflexia During Delivery in Persons With Spinal Cord Injury*

Identification Code	Level of Injury	Frankel Classification*	Delivery Route	Autonomic Hyperreflexia	Anesthesia Used
A.....	C-2	D	Vaginal	No	None
B.....	C-3	D	Vaginal	Yes	None
C.....	C-5	B	Cesarean section	Yes	Epidural
C.....	C-5	B	Cesarean section	Yes	Epidural
D.....	C-5	D	Cesarean section	No	Epidural
D.....	C-5	D	Cesarean section	No	Epidural
E.....	C-6	B	Cesarean section	Yes	Epidural
F.....	C-6	D	Vaginal	Yes	Local
G.....	C-6	D	Vaginal	No	None
G.....	C-6	D	Vaginal	No	Local
I.....	T-4	A	Cesarean section	Yes	Epidural
I.....	T-4	A	Cesarean section	Yes	Epidural
J.....	T-8	A	Vaginal	No	None
K.....	T-10	B	Vaginal	No	Local
K.....	T-10	B	Vaginal	No	Local
K.....	T-10	B	Vaginal	No	Local
L.....	T-10	A	Vaginal	No	None
M....	T-10	A	Vaginal	No	None
N.....	T-10	A	Vaginal	No	None
N.....	T-10	A	Vaginal	No	None
O.....	T-12	A	Vaginal	No	None
P.....	T-12	A	Vaginal	No	None

*See Table 2.

TABLE 9.—*Summary of Antepartum, Intrapartum, and Postpartum Complications*

	Patients, No.
Antepartum Complication	
Autonomic hyperreflexia	7
Symptomatic urinary tract infections	11
Required hospital care and IV antibiotics	2
Premature labor	2
Pressure sore with sepsis*	1
Cellulitis (from Abrasion)	1†
Bleeding (not transfused)	1
Preeclampsia (delivered prematurely)	1
Bladder stone removed at 17 weeks	1
Pneumonia	1†
Anemia, Hematocrit 0.21	1
Diabetes mellitus	1
Intrapartum Complications	
Abnormal presentation	
Transverse	2
Breech	1
Failure to progress	4
Cesarean sections‡	7
Autonomic hyperreflexia (AH)	7
Medical inductions (oxytocin)	9
Postpartum Complications	
UTI	2†
Uterine atony	2
Infected pilonidal cyst	1
AH intermittently for 5 days	1
Episiotomy dehiscence	1

UTI = urinary tract infection

*Sepsis led to bilateral below-the-knee amputations.
†Required admission to hospital and intravenous antibiotic therapy.
‡Three patients had had a previous cesarean section.

Once in the hospital, the routine care of an SCI woman must be understood by staff. Skin protection by turning the patient every two hours is essential to prevent pressure sores. The bowel program and bladder emptying method are usually well understood by the patient and should be continued except for those procedures necessary to and in preparation for delivery. Many patients reported that hospital staff did not listen to them with regard to their disability and how they manage from day to day out of the hospital.

If autonomic hyperreflexia occurs, and it will if it has in the past, it may be associated with almost any type of noxious stimuli below the level of injury. A full bladder, enema, bowel movement, uterine contractions, changing the Foley catheter, or a vaginal or rectal examination may cause it to occur. Treatment options are many but require the recognition that the symptoms and findings are intermittent and initiated by uterine contractions. Blood pressure elevation occurs most often during the stimulus time and may be accompanied by a headache with subsidence of symptoms between contractions.

Control of a dangerously high blood pressure is necessary and usually possible using epidural anesthesia for labor and delivery. Oral nifedipine, 10 to 20 mg chewed and swallowed, may be used short term for a rapid response. This may be repeated in 30 minutes if the blood pressure remains elevated. Nifedipine also can be used 30 minutes before any procedure known by history to cause autonomic hyperreflexia.[20] Blood pressure control is possible with the use of intravenous hydralazine hydrochloride or trimethaphan camsylate. The use of inhaled amyl nitrite to control autonomic hyperreflexia has been described by Verduyn.[16] Spinal and general anesthesia are also effective but are used primarily for delivery and for a limited time.

Because of poor abdominal muscle strength, vaginal delivery often requires second-stage assistance using forceps. Episiotomy closure should be with nonabsorbable sutures. Denervated areas do not absorb the catgut type sutures, which lead to sterile abscess or wound dehiscence.[1] Cesarean section in the presence of a suprapubic catheter will dictate a classic approach surgically.

Patients may continue to have uterine contractions postpartum (after pains), causing autonomic dysreflexia. A continuous epidural anesthetic approach allows for the periodic use of medication to block the signs and symptoms of the disorder, such as hypertension and headache.

In the Virginia Regional Spinal Cord Injury System, a course is taught to SCI pregnant women (and their significant other) in parenting from a wheelchair. Previous experiences of patients and staff have been well received and helpful to future parents.

The scope of this article does not permit a discussion of other important issues for women with spinal cord injuries. For those who wish more information, a book by Becker, who has T-6 complete paraplegia, provides excellent physical, medical, and psychosocial information.[21] She interviewed 19 women, who discuss their experiences and adjustment to SCI. Rabin, in *The Sensuous Wheeler,* addresses sexual adjustment after SCI. A copy can be obtained by writing to Barry J. Rabin, PhD, Suite 353, 5595 East 7th Street, Long Beach, California 90804.

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Walking After Spinal Cord Injury
Goal or Wish?

JAY V. SUBBARAO, MD, MS, *Hines, Illinois*

Less than a third of patients walk again after a spinal cord injury, whereas every one of them wants to try. Residual function, energy expenditure, the extent of orthotic support needed, and patient motivation will determine the outcome. Functional electrical stimulation and other new orthotic designs have not notably increased the number of persons able to walk after a spinal injury. Rehabilitation professionals can use patient education, illustrating relearning to walk with examples of infants' and toddlers' progress, to assist patients in understanding their abilities and limitations. The final decision on ambulation and orthotic prescriptions can be made in stages after a patient adjusts to a wheelchair-independent level.

(Subbarao JV: Walking after spinal cord injury—Goal or wish? *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:612-614)

The incidence of traumatic spinal cord injury (SCI) is 7,000 to 10,000 cases each year, with a prevalence of 150,000 to 200,000.[1] The greatest number occurs in the age group 16 to 30 years,[2] although an increasing incidence of SCI is occurring in older persons.[3] The survival after SCI has improved considerably because of better transportation techniques, efficient critical care, advances in technology, and improved urinary rehabilitation and respiratory management. The current ten-year survival rate of spinal cord injured patients is 86.3% of normal.[2]

Most SCI patients want to walk. This is important to them, and they repeatedly ask physicians, therapists, nurses, and other professionals about their chances of walking. The response to a question, "Can I walk?" should not be "yes" or "no" because there are few indicators that identify "walkers" from "nonwalkers." In this article I review the clinical criteria, psychosocial factors, and energy expenditures that should be considered in initiating a gait training program for SCI patients.

Clinical Factors Influencing Ambulatory Potential

The common clinical factors that influence a patient's walking potential after SCI are listed in Table 1.

Age

Chronologic age by itself is neither a positive nor a negative factor, but each patient's cardiopulmonary status and physical conditioning are important determinants.

Neurologic Level

The ratio of patients with quadriplegia to those with paraplegia is reported as 54:46.[2] Lesions below T-10 are associated with a higher residual functional level and a greater ability to walk. Associated injuries, a recent surgical procedure, and medical conditions affect a person's ambulatory potential. Even if a patient has residual motor function, the presence of contractures, pain, or uncontrolled spasticity will prevent walking.

Energy Expenditure

Many authors have studied the energy expenditures of paraplegic persons using different types of orthotics.[4-7] Clinkingbeard and co-workers found that a person with paraplegia expends nine times more energy per meter than a normal person walking at a comfortable speed.[8] The energy expenditure is influenced by the level of the lesion, the type of ambulation—four-point gait, swing-through gait, and so forth—walking speed, and distance traveled.

Psychosocial Factors

Most patients require assistance donning orthotic devices or direct assistance with walking itself. If the care giver is a spouse who already needs to assist in self-care activities,

TABLE 1.—*Factors Influencing Wolking Potential*

- Age
- Level of injury
  - Complete
  - Incomplete
- Associated injuries or operations, such as open reduction and internal fixation of long bone fractures or laminectomy and fusion
- Medical conditions
  - Hypertension, diabetes mellitus, COPD
  - Cardiac disease
  - Complications, such as thrombophlebitis, pulmonary embolus, decubitus ulcers
- Mechanical
  - Contractures
  - Heterotopic ossification
  - Pain
  - Uncontrolled spasticity
  - Kyphoscoliosis
- Psychosocial
  - Degree of assistance available
  - Patient's level of participation or responsibility
  - Weight fluctuations
  - Family support
  - Drug or alcohol abuse
  - Associated head injury

COPD = chronic obstructive pulmonary disease

From the Comprehensive Rehabilitation Center, Edward Hines Jr Veterans Affairs Hospital, Hines, and the Departments of Orthopedics and Rehabilitation, Loyola University Medical Center, Maywood, Illinois.

Reprint requests to Jay V. Subbarao, MD, MS, Hines VA Hospital, Bldg 1, Rm E225 (11R), Hines, IL 60141.

such as dressing and bladder and bowel care, these additional time demands may result in abandoning the use of orthoses. It is essential that the physician and the team have a good understanding of a patient's social and architectural environment.

Walking

Walking involves a translation of the body's center of gravity through a space in a *safe* manner along a pathway requiring the *least energy*. Daverat and associates found that 28% of their 157 SCI patients walked at the end of a year.[9] Maynard and colleagues in a 1979 study of 123 patients noted that, of patients with incomplete sensory deficit 72 hours after injury, 47% were ambulatory and 87% of the patients with incomplete motor lesions were "walking."[10]

Stauffer divided ambulation into four categories[11]:

- Community walker: Those patients who are able to get themselves out of a wheelchair or bed and walk for a reasonable distance in and out of their homes unassisted by another person. They may use crutches or braces and a wheelchair for exceptionally long distances.
- Household walker: Patients are able to walk within the home with relative independence but are unable to ambulate outside of the home for any significant distances and frequently use a wheelchair outside the home. Assistance may be required in getting out of bed or wheelchair.
- Exercise category: Functional mobility is attained with the use of a wheelchair. Patients require controlled conditions and considerable assistance to ambulate.
- Nonambulatory: Patients use a wheelchair entirely.

Such a classification should be used as a point of reference so that we can compare results between articles. Similarly, for the neurologic assessment, Frankel's classification is commonly used, which is as follows[2]:

- **A,** Complete lesion: complete loss of motor and sensory function below the lesion.
- **B,** Incomplete—preserved sensation only: preservation of any demonstrable sensation, excluding subjective phantom sensations; voluntary motor function is absent.
- **C,** Incomplete—preserved motor (nonfunctional): preservation of voluntary motor function, which performs no useful purpose except psychologically; sensory function may or may not be preserved.
- **D,** Incomplete—preserved motor (functional): preservation of voluntary motor function, which is useful functionally.
- **E,** Complete recovery: complete return of all motor and sensory function but still may have abnormal reflexes.

The term "incomplete lesion," although a good term for defining a neurologic deficit, is often misleading. Stover observed that 53.8% of the patients had incomplete lesions.[3] A person with C-6 quadriplegia who has voluntary extension of a toe on one side is considered to have an "incomplete" neurologic lesion, but from a functional standpoint, the patient has a complete C-6 level injury. Rehabilitation professionals should document the muscle groups that are spared and that can be used.

Rehabilitation Training for Ambulation

Every SCI patient admitted for initial rehabilitation participates in intensive physical rehabilitation and patient education. Patients must be educated about the program and its rationale. For example, patients should learn why they need to sit without arm support and the importance of this to future ambulation. All the patients are involved in a program aimed at improving trunk control, increasing sitting tolerance, strengthening the upper extremities, and retraining postural reflexes. In addition, other techniques to strengthen weaker muscles are used. The patient is advanced to standing at parallel bars with decreasing support at the trunk, pelvis, and knees. The patient starts ambulating in parallel bars with staff support and training orthoses. Patient performance at this stage is a critical indicator of future type and extent of orthotic supports and the patient's tolerance to ambulation.

Long-term Use of Orthoses

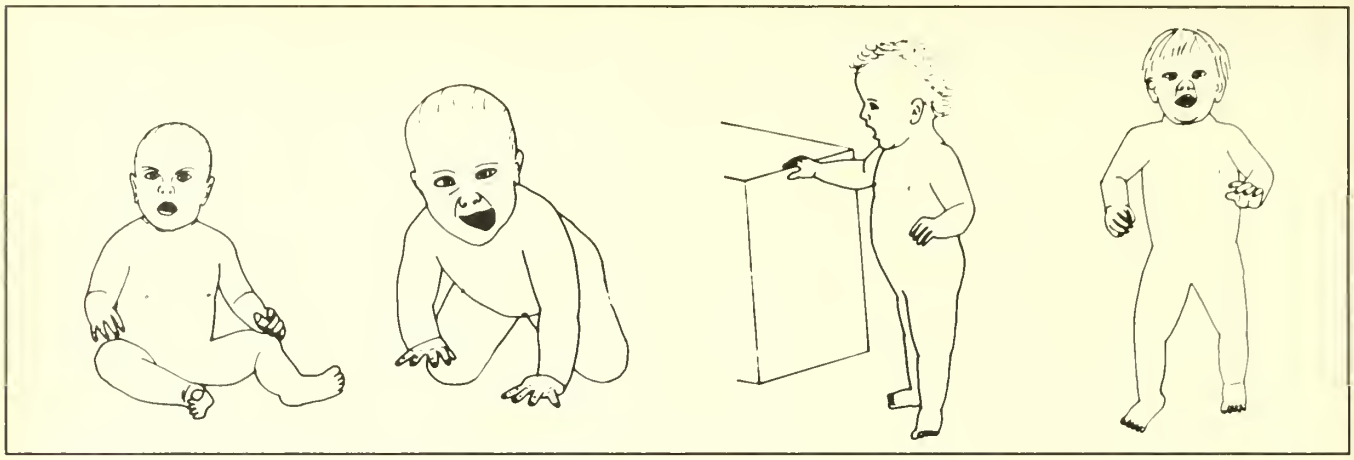
Mikelberg and Reid, in a five-year study, found that 50% of patients for whom orthoses were prescribed did not use them.[12] Only 5% of the patients routinely used their braces, and few walked. Rosman and Spira and Kaplan and associates similarly found a small percentage of patients using orthoses regularly.[13,14] Recent advances in technology and newer designs are aimed at improving the acceptance of orthoses. Successful ambulation with decreased energy expenditure has been reported using the Craig-Scott orthosis,[15] the Louisiana reciprocating gait orthosis,[16] functional electrical stimulation,[17] and a combination of orthosis and functional electrical stimulation.[18] Long-term results need to be obtained in a sufficient number of patients, using these techniques, before it can be concluded that the number of patients who can walk after SCI has increased significantly.

Who Will Walk Again?

The preceding review of clinical factors, rehabilitative process, and literature regarding ambulation in SCI establishes the fact that only a small percentage of SCI patients can be trained to become successful walkers. Few objective criteria can be applied to predetermine the "winners." Our own experience and a review of the literature[19] showed that patients became ambulatory only when they have good pelvic control, hip flexor strength of 3+, and quadriceps strength of at least 3+ on one side (muscle strength rated on a scale of 0 to 5). They also did not have contractures of the joints or uncontrolled spasticity. The patients able to walk required no more than one knee-ankle-foot orthosis and an ankle-foot orthosis on the other side. Waters and co-workers studied the determinants of gait performance in 36 SCI patients and described the ambulatory motor index derived from the manual muscle grade of both lower limbs.[20] They concluded that the ambulatory motor index influences the requirements for lower extremity orthoses and upper extremity assistive devices, that this index will determine the amount of arm work necessary as measured by the peak axial load, and that the combination of the ambulatory motor index and the peak axial load enables the potential of an SCI patient to walk to be determined clinically. Table 2 shows the neurologic deficit and type of ambulation possible. The final determinants of ambulation, however, are residual function, energy expenditure, a patient's tolerance to orthoses, the availability of a care giver, and a patient's motivation.

Is Walking a Realistic Goal or Desire?

Rehabilitation programs differ in their philosophies regarding offering trial ambulation and in prescribing orthotics. Only a small percentage of patients become ambula-



A B C D

Figure 1.—The developmental sequences of an infant learning to walk are depicted: The child sits unsupported **(A)**, crawls on all fours **(B)**, stands with support **(C)**, walks without assistance **(D)**.

TABLE 2.—*Spinal Segmental Levels and Type of Ambulation**

Neurologic Deficit Level	*Type of Ambulation*		
	Exercise	*Household*	*Community*
C-6 to C-7	yes	no	no
C-8 to T-1	yes	no	no
T-2 to T-10	yes	yes	yes/no
T-11 to L-2	yes	yes	yes
L-3 to L-4	yes	yes	yes
L-5 to S-1	yes	yes	yes

*In incomplete lesions, the type of ambulation is dependent on residual motor function.

tors, and most of those for whom orthotics are prescribed discard them soon after completing rehabilitation. Kaplan and colleagues found that the most common causes of rejecting the use of orthoses are excessive energy expenditure and the need for additional assistance to wear braces.[14] In the present cost-control environment, it is difficult to justify the expense of orthoses and the weeks of trial ambulation training. It is preferable that patients with questionable ambulatory potential be discharged independent in wheelchairs with periodic reevaluations. By that time, a substantial number of patients will accept the fact that they are not capable of walking.

Although the rehabilitation team knows that only a small percentage of SCI patients will walk, the patients are often insistent that they can walk and want to prove that the professionals are wrong. The psychological consequences of standing and walking are "Getting out of bed and being back on my feet," a sign of recovery, and "Standing up and being able to look eye to eye," a sign of confidence.

How to Respond to the Question, 'Can I Walk?'

The question, "Can I walk?" is often a great challenge to physicians and therapists. Responding simply yes or no is unwise. The patient should be engaged in understanding the task of walking and its requirements. The staff can use the developmental sequences of infants and toddlers and ask the patient to recall that an infant first learns to sit with the support of arms, then without arm support, then crawls on all fours, stands up by hanging on to objects, and eventually walks independently (Figure 1). This explanation matches the patient's rehabilitation program. It also enables the patient and staff to evaluate objectively the progress towards walking.

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To Live, to Die—Who Decides?

The Strange Death of David Rivlin

PAUL K. LONGMORE, PhD
Stanford, California

DAVID RIVLIN'S 1989 court-sanctioned, physician-assisted suicide exemplifies the social conditions that drive some disabled persons to their deaths and the ignorance and bias of some nondisabled people that lead them to support such suicides. In a 1971 bodysurfing accident in California, Rivlin sustained a spinal cord injury at the fifth cervical vertebra that made him quadriplegic, though with some use of his arms. In 1986 an operation to remove an aneurysm at the second cervical vertebra left him unable to use his arms or breathe on his own. For the next three years, he was confined to a nursing home near Detroit, Michigan. In May 1989 he petitioned a circuit court for permission to have a physician sedate him and then disconnect his ventilator. In July 1989 the court ruled that his assisted death would be nothing more than a refusal of medical treatment.*

The court ruling, the support of Rivlin's "choice" by right-to-die activists and some medical practitioners, and media accounts of this case all consistently focused on his disability as the cause of his confinement in the nursing home and his preference for death. *People Magazine* summed up that perspective when it described his disability as "his ultimate imprisonment" and said that it reduced him to "a cruel semblance of life" (August 7, 1989; 32:56). This viewpoint misstated the basic issues and misread much of what Rivlin himself said.

"Life is more than surviving," said Rivlin a few days before his death. "It's interacting with other people, it's having a family, it's having a career, it's having a wife. It's all of those things and I can't have them. . . . I've tried to figure out other ways but there is none" ("Accident Victim: Life More Than Surviving," *Daily Reporter* [Coldwater, Michigan], May 20, 1989, p 2).

In fact, David Rivlin could have had a chance at all the things he wanted, but current public policies cut him off from them and sentenced him to a nursing home. A crippling system, much more than his disability, denied him any self-determination and finally made his life unbearable. Tens of thousands of physically disabled young adults find themselves trapped in nursing homes. The disability rights movement has fought to liberate them. In states like California, people with disabilities much like Rivlin's live in their own homes, raise families, attend school, and hold jobs. Their independent and productive living is partly the result of California's In-Home Support Services program. It provides financial aid for housekeeping and assistance with personal needs.

David Rivlin tried to live independently in Michigan. He hired live-in aides. But the maximum amount Michigan grants disabled people to pay chore workers to do housekeeping and assist them with tasks such as bathing, dressing, and eating is $666 a month. And disabled people have to fight for that much. Many get much less. Rivlin reportedly received less than $300 a month (*People Magazine*, August 7, 1989, p 58; M. Johnson, "Drab Curtains," *Disability Rag*, September-October 1989; 10:24). That averages out to less than $10 a day or about $0.41 an hour. For that amount, no quadriplegic person can find a competent and responsible chore worker. No wonder Rivlin kept failing in his attempts at independent living.

It is not that Michigan cannot afford to fund independent living. It paid the nursing home $230 a day to keep Rivlin locked up (*Detroit News*, May 19, 1989, p 1-A). Independent living at an adequate rate of, say, $50 a day would have been much cheaper. More important, it would have given Rivlin the freedom he yearned to recapture. It would have given him a chance to realize his dreams.

In 1980 Rivlin met Zoe Dixon, a nondisabled woman. They fell in love and got engaged. He moved into her home. According to Rivlin, "It lasted about a year. The burden of my being a quadriplegic broke us up" (*People Magazine*, August 7, 1989, p 58). No reporter asked what he meant by "burden." No one in contact with him understood enough about disabilities to ask the right questions about his relationship with Dixon: Did she act as his aide? Was she his only aide, or did she get some respite? Could he call on paid workers so that he was not exclusively dependent on her? Did they know that their marrying would jeopardize the meager amount he could get from the state to hire personal assistance workers? Did they therefore keep their relationship secret from government social service agencies? No one—no reporter, nor the lawyer who filed Rivlin's request-to-die petition, nor the physician who aided his suicide—knew enough about him or physically disabled people to ask such questions.

Rivlin had other dreams besides marriage and family. He majored in philosophy in college and wanted, according to varying accounts, either to teach philosophy or to become a psychotherapist. But, according to one reporter, "his dreams disappeared as he was pounded and torn by the churning surf" in his 1971 accident. In fact, from 1974 to 1979, Rivlin continued to pursue his education at Oakland University in Michigan.† Neither his spinal cord injury nor even his later use of a ventilator need have destroyed his professional dreams. What blocked their fulfillment were the obstacles to independent living the system threw in his way.

At least when he was trying to live independently, he could hope that he might one day realize those dreams. At

*J. A. McClear, "A 'Driving Wish' To Die," *Detroit News*, May 19, 1989, Life p 1-A, 6-A; J. Neubacher, "Whose Life Is It, Anyway?" *Detroit Free Press*, May 29, 1989, p 5-A; M. Dougherty, S. R. Tessler, "Controversy: Tiring of Life Without Freedom, Quadriplegic David Rivlin Chooses to Die Among Friends," *People Magazine*, August 7, 1989; 32:56-58

†*Detroit Free Press*, May 29, 1989, p 5-A; *People Magazine*, August 7, 1989, p 58; *Detroit News*, May 19, 1989, p 1-A.

(Longmore PK: The strange death of David Rivlin. *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154: 615-616)

Paul K. Longmore, PhD, is Visiting Assistant Professor of History at Stanford University and a disability rights activist. He uses a ventilator as a result of polio.

Reprint requests to Paul K. Longmore, PhD, Department of History, Stanford University, Stanford, CA 94305-2024

first in the nursing home he clung to the hope that he might escape. At last his imprisonment made him despondent and despairing. "In the last two years, I never once found him reading or listening to music or talking to someone," a friend recalled. "He just lay there, looking straight up at the ceiling or dozing" (*People Magazine*, August 7, 1989, p 58).

"I don't want to live an empty life lying helplessly in a nursing home for another 30 years," Rivlin said. He came to realize that he would have "to spend the remainder of my life in an institution. . . . What pushed me over the edge was the realization that I was anchored to one spot." "If you're in a situation where you have no freedom," he said, "then you have to make a change, and my change is death."*

Despite the emotional battering Rivlin suffered, he received no psychological counseling during the two years before his death. A court-appointed psychiatrist concluded he was competent, yet Rivlin's lawyer refused to say what, if any, qualifications the psychiatrist had in the psychology of disability, a specialized field.† Rivlin was denied appropriate psychiatric evaluation and crisis intervention counseling. The nondisabled people around him assumed that when a person with such a disability said he would rather be dead, he must be acting rationally. No one helped him search for, in his words, "other ways" than suicide. The denial of appropriate counseling surely contributed to his death. It is a central issue in this case.

The conditions that led David Rivlin to prefer death have been factors in other assisted suicide cases involving disabled persons that have captured media attention. Elizabeth Bouvia in California, Larry McAfee in Georgia, and Kenneth Bergstedt in Nevada were all denied appropriate psychological diagnosis and counseling. Bouvia and McAfee were deprived of adequate financial support for independent living. The only real aid the system offered any of them or Rivlin was assistance in ending their lives.

These cases contain three lessons for health care professionals: First, saving people's lives, rehabilitating them, and teaching them the medical and physical management of their now-disabled bodies is pointless if they are denied the right and the means to control those lives. Health care professionals must support the disability rights movement's efforts to secure adequate, nationwide, government funding for self-directed independent living.

Second, health care professionals should not assume that suicidal gestures are simply a response to a person's physical disability. Social factors—segregation, the denial of self-determination, cultural devaluation—are always present and typically primary in generating such despair. For that reason, disabled people undergoing emotional crises must receive psychological evaluation and counseling from appropriately trained therapists.

Third, until people with major disabilities are guaranteed their rights to self-determination, independent living, equal access to society, and appropriate psychological counseling, medical professionals must never support or assist the suicide of a disabled person. To do so in the present societal circumstances of devaluation, discrimination, and segregation is simply the ultimate act of oppression.

People Magazine, August 7, 1989, p 58; *Detroit News*, May 19, 1989, pp 1-A, 6-A; "Court OKs Death Wish," *USA Today*, July 7, 1989, p 2-A

†*Detroit News*, May 19, 1989, p 6-A, United Press International, "Man Disabled 18 Years Seeks Doctor to Cut Off Life Support," *Indianapolis Star*, July 7, 1989, p A-11; D. B. Piastro, "He Needed Help to Live," *Long Beach Press-Telegram*, August 1, 1989, p C-2.

A Disability Rights-Independent Living Perspective on Euthanasia

ANDREW I. BATAVIA, JD, MS*
Washington, DC

THE ISSUE OF WHETHER euthanasia should be legalized in this country has been debated extensively from a wide variety of perspectives.[1,2] Seldom, however, is it addressed from the viewpoint of persons with severe physical disabilities who wish to maintain autonomy over the fundamental decisions that affect their lives. It is from this important "disability rights-independent living" perspective that I hope to contribute to the debate.

For purposes of clarity, it is valuable to state explicitly at the outset what I do not address in this article. First, I do not address whether there should be a right for disabled people to refuse treatment—to disconnect life-support systems such as ventilators or feeding tubes—sometimes referred to as "passive euthanasia." This right has been recognized by many courts[3] and is implicitly accepted in this article. Second, I do not address "involuntary euthanasia," in which there is no request by a person to terminate his or her life. The legality and morality of this practice, which is regarded as tantamount to genocide by some segments of the disabled population,[4] must be addressed elsewhere.

Thus, in this article I address only "voluntary active euthanasia" in the disability context—whether a legally competent person with a disability (that is, a functional limitation not necessarily associated with any illness, terminal or otherwise) who wishes to die should have the right to assistance in actively terminating his or her life. While different people with disabilities differ on this issue, I believe that the view expressed here is most consistent with the philosophy of the disability rights and independent living movements—social movements initiated in the early 1970s by disabled people to pursue their legal rights and to remove environmental barriers that limit their ability to live independently in their communities.[5]

People with disabilities have an interest in the legalization of voluntary euthanasia even greater than that of the nondisabled population. Many people with disabilities have substantial functional limitations that significantly reduce their ability to live independently. Many experience severe pain or discomfort that prevents them from engaging in productive or recreational activity. After months or years of contemplating their situations, some wish to die but are unable to commit suicide without assistance. Such assistance would constitute euthanasia, which is considered murder under our legal sys-

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Andrew Batavia is the Associate Director for Health Services Research of the National Rehabilitation Hospital Research Center (NRH-RC) and a member of the faculty of the Georgetown University School of Medicine. He recently was awarded a 1990-1991 White House Fellowship and currently is on leave-of-absence from the NRH-RC while serving as a Special Assistant to the Attorney General. The views expressed in this article are solely his own and do not necessarily represent the position of any organization or government agency.

Reprint requests to Andrew I. Batavia, 700 7th St, SW #813, Washington, DC 20024.

tem, and which, therefore, would subject the person who assisted them to legal jeopardy.

As a person with a physical disability (C2-3 quadriplegia), and as a researcher and attorney who studies health care and disability policy, I have strong feelings about the right to euthanasia. Since I was injured at the age of 16 (approximately 18 years ago), my most important objective has been to gain the fullest possible control over my life. This goal is not very different from that of many nondisabled people, but it is somewhat more difficult to achieve for people with no voluntary use of their arms, hands, and legs. Through advanced education and professional endeavors, I have been able to obtain substantial control of my life and, consequently, substantial satisfaction and happiness.

Unfortunately, many disabled people have not had these opportunities, and some live unhappy lives in which they have (or at least believe they have) little or no control. Three of my friends decided several years after becoming disabled that they no longer wished to live and committed suicide. One attempted suicide three times over a five-year period, twice wounding himself severely and painfully before successfully killing himself. All three ultimately were able to free themselves from lives they did not want. All three had sufficient functional capacity to complete the act without any assistance. For other disabled people who do not have such capacity, suicide is impossible. For them, voluntary euthanasia is the functional equivalent of suicide.

The ability to choose whether to commit suicide—to implement the decision to continue or discontinue life—constitutes the ultimate manifestation of control over one's life. People who believe they have no control over the fundamental decision to live cannot claim to have autonomy over their lives. Possibly in recognition of this, and because it is considered ludicrous by many to punish an attempt at taking one's own life, attempted suicide is no longer illegal in this country. We respect, or at least tolerate, the decision of a person capable of suicide to take his or her life. Yet we continue to prohibit people incapable of suicide from having another person assist them.

Beyond the various religious arguments, the primary contention against the legalization of voluntary euthanasia concerns its potential for abuse—that is, actual murder or emotional coercion to choose death. Appropriate safeguards to prevent such abuse can be built into a law permitting euthanasia. In the Netherlands, for example, there is no prosecution of euthanasia if a specific protocol is followed involving confirmation of the request made to more than one physician by the person wishing to die.[6,7]

In reality, the prohibition against voluntary euthanasia in our society is based primarily on social paternalism. People with terminal illnesses or severe disabilities are considered by society incapable of making a rational decision to die. Yet, in truth, most disabled people are at least as capable as nondisabled people of making such decisions and, in the interest of self-determination, should be allowed to do so. As a person with a disability, I resent the prospect of physicians, judges, or public officials making decisions about me that are inherently personal and that fundamentally affect my life. Many other disabled people, as well as many nondisabled people, share this sentiment.

Thus, in the interest of autonomy and self-determination, voluntary active euthanasia should be legalized in this country. First, however, we must provide disabled people with the supports they need to live in a dignified manner. Many disabled people require substantial resources, including personal assistance services, to live in their communities.[8] Some are discouraged by national and state policies from attempting to live productively and independently.[9] Without adequate resources and incentives, disabled people are given little reason to live. Many who are choosing suicide are responding rationally to a system that does not provide the supports they need (G. Kolata, "Saying Life Is Not Enough, the Disabled Demand Rights and Choices," *New York Times*, January 31, 1991, p B-7). Some do not want to live because they think they are imposing enormous caretaking and financial burdens on their families and friends.

Contrary to common belief, the vast majority of people with disabilities cherish life and are content to live with their disabilities until their natural deaths. It is likely that few would choose euthanasia if they had viable alternatives to meet their needs and to live with dignity. As a society, we must provide such alternatives. For those who ultimately decide that they do not want to live, we must respect their choice.

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Responding to Requests for Ventilator Removal From Patients With Quadriplegia

FREDERICK M. MAYNARD, MD
Ann Arbor, Michigan

RECENT ADVANCES IN MEDICAL TECHNOLOGY and the availability of emergency medical services have allowed an increasing number of people to survive serious injuries and catastrophic illnesses that permanently impair respiratory function and that require the lifelong use of mechanical ventilation. Spinal cord injury centers have developed remarkably effective special programs for the comprehensive rehabilitation of patients with high quadriplegia who require ventilator use.[1,2] During follow-up interviews after rehabilitation dis-

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From the Department of Physical Medicine and Rehabilitation, Model Spinal Cord Injury Care System, University of Michigan Medical Center, Ann Arbor.

Reprint requests to Frederick M. Maynard, MD, Department of Physical Medicine and Rehabilitation, NI-2A09-0491, Model Spinal Cord Injury Care System, University of Michigan Medical Center, 300 N Ingalls Bldg, Ann Arbor, MI 48109-0491.

charge from one of three such centers, 26 (87%) of 30 patients were residing outside an institution, 28 (93%) reported "being glad to be alive," and 19 (63%) rated their quality of life as good or excellent.

Despite these results and perhaps in response to greater societal interest in avoiding futile medical treatment, requests for ventilator removal by patients with quadriplegia who require ventilator use have become more frequent (M. Johnson, *Disability Rag*, September-October 1990, pp 16-26; P. Painton, E. Taylor, *Time*, May 19, 1990, pp 62-71).[3,4] A broad spectrum of factors may contribute to a person's making such a request. Hopelessness and despondency about the future are common emotions. Although the origins for these feelings may be unique to each person's attitudes, values, and previous life experiences, inadequate resources for creating an acceptable life-style can also be the primary source for the desire to die. Thus, it can become difficult for health care professionals to discriminate between requests that reflect a reactive depression and those that represent the existential decision of a competent adult person. Because recent court decisions have made it clear that competent people do have the right to refuse medical treatment, including continued ventilator use,[5(pp2-4)] physicians should plan in advance how to respond to patients' requests for this action.

Health care professionals responding to a request for ventilator removal by a person with quadriplegia must consider their own attitudes about the value of life for people with severe physical disability. Able-bodied people respond sympathetically to a request for ventilator removal because they may assume that they would feel the same if in similar circumstances. Nevertheless, it is important to consider the distinction between a request for permission to commit suicide by a patient with quadriplegia who does not require ventilator use and a request for ventilator removal by one who does. Some members of the independent living movement for people with physical disability have suggested that there is no competent person whose physical disability is so extensive that the person could not end his or her own life without assistance from another person. They assert that withdrawing life-sustaining treatment from people with a stable, if severe, physical disability reflects an attitude of discrimination toward and devaluation of people with disability (A. Ruggeberg, Gazette International Networking Institute's Fifth Annual Conference on Independent Living and Post-Polio Rehabilitation, oral communication, June 3, 1990).

With sensitivity to this position and the historic commitment of the medical profession to preserving life, a simplistic affirmative response to a request for ventilator removal by an apparently competent patient with ventilator-dependent quadriplegia is inappropriate. The first consideration before formulating a response to such a request is determining whether the patient is expressing suicidal ideation or has made a thoughtful choice to discontinue life-sustaining treatment. There is an important distinction between these two. In the study previously cited of patients with high quadriplegia using ventilators, 50% reported suicidal ideas, such as "wishing to be dead."[1] By contrast, it is unusual for a patient to state clearly and emphatically, "I want to be taken off the ventilator now, and I know what this means." Health care professionals frequently ignore initial requests for ventilator removal because they are uncomfortable dealing with such requests. Responding to a serious request for ventilator removal in the same way as responding to suicidal ideas may appear to trivialize such requests and offend the patient. Responding to requests for ventilator removal by discussing the common occurrence of death wishes can be helpful and can reassure a despondent patient. Misinterpreting a thoughtful request as an expression of temporary depressive thoughts must be avoided.

When it is clear that a patient is serious about requesting ventilator removal, it becomes important to acknowledge the legal right of patients to refuse medical treatment. United States courts have consistently ruled that competent patients with unremediable conditions requiring ventilator use have the right to be removed from ventilators.[5(pp2-4)] The purpose of acknowledging this legal right, as a patient's attending physician, is to avoid a battle of wills. When a physician says, "We cannot allow you to do this," a person's resolve to be removed from a ventilator is more likely to increase. This response accentuates feelings of loss of control, and these feelings are high among people with extreme physical dependency. By acknowledging their right, physicians will not unintentionally encourage patients to pursue proving they ultimately have the legal right to decide their own fate. Furthermore, if a battle of wills can be avoided from the beginning, some people may get through their hopelessness and change their mind about wanting to live. The case of McAfee (P. Painton, E. Taylor, *Time*, May 19, 1990, pp 62-67) supports this view because he has so far chosen not to discontinue ventilator use after successfully pursuing permission from the Georgia Supreme Court to do so. Distressed patients may occasionally try to gain sympathetic attention from family or care givers with an expressed wish to die. Taking these patients' requests at face value can sometimes expose their manipulative purpose.

After discussing the right to refuse continued treatment, I usually recommend that several action steps be followed by the patient and by the attending physician before a request for ventilator removal be honored in order to preserve the ethical integrity of the medical profession and to maintain respect for a patient's autonomy.

Action Steps for Patients

- Obtain independent legal counsel. Most patients and families know how to do this and only need permission and encouragement to do so. Other patients may need help to find legal counsel, and fees may be problematic.
- Discuss the request with family, significant others, and spiritual counselors. The patient must be given ample opportunity to communicate thoughts and emotions with as many people as possible about his or her current condition and available options for the future.
- Meet with peers and learn about their lives. A peer is a person who has a similar physical condition and ideally is of the same sex and social, economic, and educational background. Although it can be difficult to find a perfectly matched peer, anyone who is living successfully while continuing to use a ventilator can be helpful, and it is critically important that the patient meet and communicate with such people.
- Learn about all possible rehabilitation outcomes. Patients and families must have exposure to a wide variety of educational resources about and options for rehabilitation. Possible goals for rehabilitation and independent living, and the process needed to reach them, must be explained and understood.

• Participate in independent psychological evaluations. These assessments must be done to establish a person's competency for making decisions about his or her own welfare. Patients must comply with these interviews and demonstrate knowledge about their condition, the implications of having their request granted, and about all available options for continued care.

Action Steps for Attending Physicians

• Consult with a medical ethics committee. Most hospitals today have a multidisciplinary medical ethics committee. Members of these committees can provide emotional support for professionals, address both moral and legal concerns, and provide insights from many perspectives.

• Discuss plans and concerns with all members of the health care team. It is vitally important that everyone involved with a patient's care understand what is happening and that all team members work together. Everyone's feelings need to be acknowledged, and all must be reassured that they will not be asked to violate their own moral integrity.

• Maintain communication with the patient and family. If dialogue continues, every opportunity for the person to retract the decision to die can be ensured. All interested parties can also make their concerns known, and severe emotional pain after the termination of life support can be lessened.

• Enable patients to complete their action steps. They may need considerable support and firm encouragement to engage in these action steps. They may also need assistance and resources to complete some of them.

• Formulate an opinion about a patient's capacity for making decisions about his or her own welfare. The Hastings Center has recommended that a "process standard" be used for determining the capacity to make such decisions.[5(pp130-133)] Health care professionals may have appropriate concerns that a patient's decision is a result of temporary reactive depression. The patient may not be able to evaluate the situation rationally and make a competent decision that is not simply reflecting feelings of hopelessness. Applying the process standard can ensure that a decision is responsible and well thought out. By giving the patient some action steps to carry out, the physician can observe the patient's behavior over time. During this time, when an attorney is contacted, interviews take place, information is provided, and a discussion occurs with other people, the patient's capacity to understand available choices and the implications of the decision can best be determined by the attending physician and the health care team.

In summary, there is therapeutic value in respecting patients' autonomy and right to refuse treatment as an initial response to requests for ventilator removal by patients with ventilator-dependent quadriplegia. Knowledge that the decision is ultimately their own may make such patients more likely to change their mind with the passage of time. Nevertheless, patients with strongly expressed desires to withdraw mechanical ventilation may have a high probability of dying regardless of what action is taken by professionals. Patients who have mechanical ventilation withdrawn and who reject the quality of life offered by medical rehabilitation may create strong feelings of futility and low self-worth among health care professionals whose work strives to enhance the quality of life for these patients. The paradigm of independent living, however, emphasizes the central role of individual self-determination, irrespective of complete physical helplessness.[6] Therefore, when persons who have tested life with ventilator-dependent quadriplegia after optimal rehabilitation or who have thoughtfully considered all of their options make a responsible choice to withdraw treatment and end life under these circumstances, the decision can be viewed as consistent with the traditional goals of medical and rehabilitative practice.

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Living With a Ventilator

IRENE S. GILGOFF, MD
Downey, California

"I'M NO DIFFERENT from you. I'm just sitting down."[1] The statement was made by a 25-year-old man with Duchenne's muscular dystrophy during a taped interview with a psychology student. On initial inspection, his gaunt face led the interviewer to think that there were many differences between them—many more than simply their position in space at that moment. The powered wheelchair that he controlled with his tongue and that held the mechanical ventilator beneath its solid frame made their lives seem more different than anything they could possibly have shared. Yet as the interview progressed, they found that they shared many of the same dreams, goals, and interests. Music gave each great comfort. And relationships with people had caused both the greatest pains and the greatest pleasures in life. The soft hum of the ventilator as it momentarily interrupted his speech became less noticeable as the interview progressed. Indeed, he also became less different. His life, though more arduous, was one that he valued no less than the interviewer valued his own. He wished that his choices had included whether he needed to have muscular dystrophy or not, but that was never an option. The choice as to whether he wanted to continue his life by using a ventilator when his muscles failed him—well, he made that choice, and he did not regret it.

The use of a ventilator as a treatment modality for patients with chronic disease began with the polio epidemics of the 1940s and 1950s.[2] For many patients with acute respiratory failure of polio, reality became life forever dependent on a machine. Many of these survivors went on to find successful

(Gilgoff IS: Living with a ventilator. *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:619-622)

From the Department of Pediatrics, University of Southern California School of Medicine, Los Angeles, and Rancho Los Amigos Medical Center, Downey, California.

Reprint requests to Irene S. Gilgoff, MD, Dept of Pediatrics, Rancho Los Amigos Medical Center, 7601 E Imperial Hwy, Downey, CA 90242.

careers, and many have raised families. Today, they serve as inspiration to a new generation of survivors.

With the treatment of polio as the prototype, the use of the ventilator to assist patients with other neuromuscular diseases soon followed. Patients with Duchenne's muscular dystrophy,[3] spinal muscular atrophy,[4] amyotrophic lateral sclerosis,[5] and congenital myopathies[6] are now given the options of prolonging their lives after their respiratory muscles fail. Patients with traumatic injury to the cervical spinal cord,[7] central hypoventilation syndrome of childhood (Ondine's curse),[8] and primary pulmonary diseases such as chronic obstructive lung disease[9] are also finding assisted mechanical ventilation to be a long-term treatment option.

Treatment Options

When long-term assisted mechanical ventilation is considered, the goal of prolonging life must carry with it an equal obligation to ensure improving the quality of life. To achieve both goals, the best treatment option is one that interferes least with a patient's life-style. Return to the home environment and continued participation in fulfilling community pursuits is a prerequisite to success. Decisions as to which system of ventilation is best must be tailored to each patient, with consideration given both to the medical needs of the patient and to the patient's life-style.

The negative-pressure ventilation systems of the polio era continue to be an alternative today (Figure 1).[10] In some patients, it is possible to postpone tracheostomies through the use of negative-pressure systems: the iron lung, body cuirass (Figure 2), or pneumobelt. Because of their lack of portability, they are most commonly used in patients dependent on assisted ventilation for nighttime only.

A tracheostomy may be necessary, however, in a patient with a neuromuscular disorder who lacks a functional cough or who has recurrent aspiration.[4] In these patients, the use of an uncuffed tracheostomy tube will allow them to speak. In most cases, patients with tracheostomies are able to resume previous eating habits. In patients who require fulltime ventilator support, tracheal positive pressure continues to be the system that offers the greatest degree of control of ventilation. Recent developments in positive-pressure ventilation now also offer alternatives for patients dependent on nighttime assisted ventilation that avoid the use of a tracheostomy, such as mouth[11] or nasal[12] positive pressure.

Figure 1.—The iron lungs of the polio epidemic era are examples of negative-pressure ventilation (photograph courtesy of Rancho Los Amigos Medical Center, Downey, California, and the March of Dimes Birth Defects Foundation).

Figure 2.—The cuirass shell (Lifecare, Inc) provides negative-pressure ventilation.

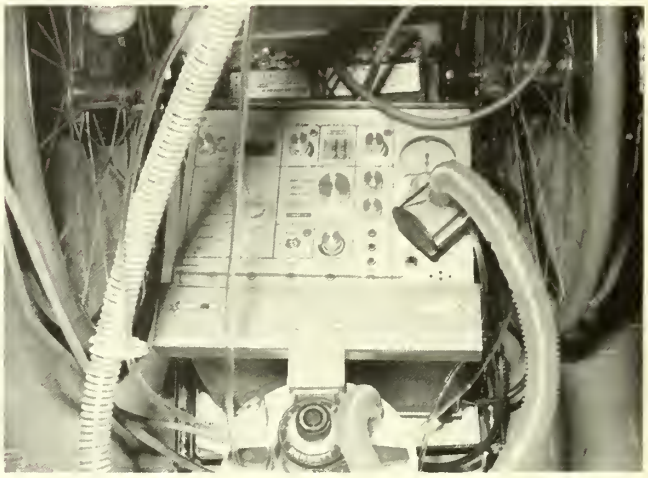

Figure 3.—A portable positive-pressure ventilator can be fitted to a wheelchair.

Positive-pressure systems have the advantage of portability because they fit easily beneath a manual or powered wheelchair (Figure 3). Internal batteries allow about 1 to 2 hours of time off electrical current, but when supplemented with an external battery, battery time increases to as long as 20 hours.

When to Begin Using a Ventilator

In many patients, the prediction of respiratory failure is impossible. An unconscious trauma victim is intubated and ventilated before the diagnosis of high cervical cord injury can be confirmed. In a patient with a neuromuscular disorder, even though acute respiratory failure is usually preceded by years of gradual decline, the actual occurrence of respiratory failure may be insidious. With close follow-up, however, impending respiratory failure often can be predicted. Prediction is of utmost importance because it allows time to educate the patient, who is then able to make a choice regarding whether medical intervention with the ventilator is desirable.

Predictive indicators may vary by diagnosis. For example, vital capacity has been of predictive value in Duchenne's muscular dystrophy[13] but not helpful in spinal muscular atrophy.[4] Hypercapnia is also seen in Duchenne's disease, whereas in spinal muscular atrophy where chest wall collapse is common, respiratory failure presents more commonly with hypoxia. In some patients, recurrent pneumonia is a valid indicator of impending respiratory failure.

In patients with neuromuscular disorders, the common factor is that respiratory failure is due to weakness of the respiratory muscles that is inherent to the disease. Inherent also is that the course of most of these disorders is progressive deterioration. Therefore, any indication of respiratory insufficiency is a serious harbinger of impending respiratory failure.

When impending respiratory failure can be predicted and treatment is desired by the patient, elective intervention becomes possible. Early intervention prevents the repeated readmissions to medical intensive care units frequently necessary in these patients.

Many patients begun on assisted mechanical ventilation as an elective procedure are able to be weaned from fulltime dependence to nighttime use only. Theories on the value of resting fatiguing respiratory muscles[14] find support in examples of patients who have been successfully maintained on nighttime assisted ventilation for many years.[4,6] Few or no life-style adaptations are required in these patients following the addition of the ventilator.

Living With a Ventilator

Many articles document the ability to prolong life through the use of a mechanical ventilator. Patients with Duchenne's muscular dystrophy are surviving into their 40s, having been on assisted mechanical ventilation for upwards of 20 years. Patients with spinal muscular atrophy who survived respiratory failure in the first decade of life are also now alive in their 30s and are continuing to live active and productive lives.

Many of these patients are proving that the possibility of a satisfying life exists for those dependent on a ventilator. Many children have been successfully mainstreamed back into their neighborhood schools. Public Law 94-142 has allowed these children to be reintegrated into a school environment that enables them to share educational and social experiences with their nondisabled peers.[15] Many have graduated from college and, with the benefit of our increasingly technology-dependent world, are finding successful employment. Examples of successful career endeavors include that of noted Cambridge University physicist Stephen Hawking, who is ventilator-dependent from amyotrophic lateral sclerosis. The new Americans With Disabilities Act promises even broader horizons and establishes a national commitment to the disabled population.[16]*

Even with all these examples, controversy continues to surround the use of a mechanical ventilator for long-term purposes. Arguments focus on whether a ventilator prolongs a person's life or a patient's death. The ventilator can assume both roles. Distinguishing the roles is the ethical dilemma faced by physicians, patients, and family. A parent and daughter poignantly wrote of how these separate roles of the ventilator touched her life:

> Four years ago I was immersed in the medical community. My 8-month-old daughter was diagnosed as having Werdnig-Hoffmann disease (spinal muscular atrophy). The next 15 months, my daughter was hospitalized for pneumonia four times. For this reason, [her doctors] recommended that she be given a tracheostomy and use a ventilator when she sleeps. The decision was . . . difficult. . . . She obviously could benefit greatly from the positive aspects of the tracheostomy-ventilator combination, but the prospect of her disease progressing until she was completely immobile and kept alive by the ventilator was frightening. We took the risk. We chose to move with the hope that this intervention would give her more chance to have a happy "normal" life.
>
> Joelle has had her tracheostomy for three years and uses the ventilator only when she sleeps. She is much stronger now. She goes to regular kindergarten, zips around in her power chair, and goes everywhere with us. She has gained weight. She is a pretty, fun-loving child and gives more joy and love than she takes. . . . Thank God for her ventilator and the doctors who encouraged us to give it to her.
>
> Last year I had to face a different scenario. My father had suffered a stroke five years prior. He had not been able to accept the limitations it gave him and he became more and more irritable and sickly. . . . my mother was having to give him more and more care. Last March he felt bad, walked to the car, collapsed and stopped breathing as my mother drove him to the emergency room. He was resuscitated and put on a ventilator but never regained consciousness. Subsequent EEG readings showed only alpha waves. If he did recover, there would be significantly more damage to his body. . . . [and] he would [be] even more miserable than before. My mother was in anguish. I knew my father would not want this for her.
>
> My daughter's doctors had taught me that my opinions are valuable. They gave me the confidence I need to take care of my daughter at home. That confidence motivated me . . . toward letting my father die in peace.
>
> Through the hospital ethics committee, we started action to take my father's body off artificial life support. . . . For 24 hours after the ventilator was removed, my father's body continued to breathe, and then stopped. My father was at rest, and so was my mother (M. J. Inoueye, written communication, September 1990).

Use of the ventilator in the acute care setting where the goal is the return of functional breathing by the patient is a procedure almost universally accepted. It is only when the goal of treatment becomes the replacement of normal physiologic breathing with the long-term use of a mechanical ventilator that ethical issues often cloud the medical discussion. Physicians look for the answer to the question of whether a ventilator prolongs life or death in medical textbooks but often find the answer more clearly in the hearts of the patients and families confronted with this decision.

The *Tao Te Ching*, a book of Chinese philosophy, says,

> In caring for others and serving heaven,
> There is nothing like using restraint.
> Restraint begins with giving up one's own ideas.[17(verse59)]

Applying this maxim to Western medicine, physicians in their ethical query of whether or not a mechanical ventilator is a viable treatment option for a particular patient are obligated to understand the possibilities that a ventilator offers. They then become the educators of patients and must allow patients and their families to take these possibilities and to apply them to their own lives, creating their own vision of the future.

*See M. Golden, "Americans With Disabilities Act—Implications for the Medical Field," pages 522-524 in this issue, for a discussion of the act.

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Refusing Treatment During Rehabilitation

A Model for Conflict Resolution

KATHELEEN REIDY, PhD
KELLEY S. CROZIER, MD
Philadelphia, Pennsylvania

THE GOAL OF REHABILITATION MEDICINE is to enable physically disabled patients to achieve optimal self-sufficiency and function. Care is provided by a multidisciplinary team, with the patient being an integral team member. Rehabilitation is often lengthy, with inpatient programs lasting as long as six months. During this time, patients must cope with life-altering disabilities that may be irreversible. It is not surprising that treatment refusals arise in this setting.

Ethical Decision-Making Models in Medicine

The historical model for medical decision making is paternalism. This model assumes that physicians, with their specialized knowledge, skills, and experience, are best able to determine appropriate medical intervention for patients. This model fails to acknowledge patient autonomy and has largely been replaced by the contractual model of informed consent.[1] Under this view, a physician is morally responsible for providing only that care which has been mutally agreed on by the patient and physician.

For several reasons, medical ethicists have raised questions about the applicability of the contractual model of informed consent in rehabilitation.[1] Rehabilitation is inherently a team effort requiring the coordinated services of a variety of health care specialists who share authority and responsibility. Rehabilitation is accomplished over an extended period of time, thus allowing ethical concerns to evolve and be played out fully. Interpersonal conflicts may therefore become more prominent. In addition, rehabilitation rarely yields "cures," and life-saving strategies are less frequently implemented. Ethical and medical concerns are more amorphous, encompassing many aspects of a patient's life. It may be difficult for patients to see the causal relation between weight shifts and the prevention of decubitus ulcers or between range-of-motion exercises and the prevention of contractures. Given the sudden occurrence and catastrophic nature of some disabling conditions, patients and families frequently cannot immediately integrate information about the injury and comprehend long-term ramifications of treatment. The capacity for "informed consent" (or refusal) may thus take time to develop.[1]

The Educational Model

Given the limitations of the contractual model in a rehabilitation setting, an alternative "educational" model to guide patient-provider relationships has been proposed.[1] Implicit in this model is the belief that a sudden, life-altering illness or injury may render a patient temporarily unable to make fully informed decisions regarding treatment. The weighing of options and potential ramifications of choices may be difficult during the early stages of accommodating to disability. Under the educational model, a physician has greater leeway to guide decision making during the early phases of rehabilitation. The restoration of the patient's ability to make autonomous decisions regarding care is viewed as an evolutionary process. Key elements in the process are patient and family education, experience in therapy, and frequent opportunities for discussions with care providers. An external review committee to monitor the patient's status is also vital.

Despite an allowance for paternalism early in the rehabilitation process, the educational model stipulates that informed consent is necessary if potentially life-threatening treatments or procedures are recommended. Attempts should be made to accommodate patient requests whenever feasible. Patients always retain the right to legal counsel, if desired. The guiding principle in the educational model is not to limit a patient's rights but rather to restore full autonomy through education and appropriate physical and emotional care.

Treatment Refusals in Rehabilitation

When patients reject, refuse, or challenge treatment recommendations that the team thinks are vital, a crisis can be precipitated. Medically necessary care to prevent the development of a life-threatening illness or treatment that would ultimately improve a patient's quality of life may be refused. These refusals by "difficult patients" challenge staff members' views of themselves as benevolent, selfless care givers and can engender staff dissension and discontent.

When a refusal crisis occurs, the rehabilitation team must determine the reasons for the treatment refusal and develop a rational, caring response. The patient's medical needs and personal wishes should be identified and clarified, and the patient's decision-making competence may need to be formally assessed. Severely impaired cognitive processing due to a thought disorder, affective disorder, or central nervous system impairment may result in incompetence, but these conditions are present in only a small portion of patients who refuse treatment.

Stereotypic beliefs about patients must be avoided. For example, the team may assume that a treatment refusal reflects emotional turmoil that is clouding judgment. The team may even view this as suicidal behavior by a patient. While

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From the Thomas Jefferson University Hospital, Philadelphia, Pennsylvania.

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Reprint requests to Katheleen Reidy, PhD, Thomas Jefferson University Hospital, 111 S 11th St, Suite 9604, Philadelphia, PA 19107.

depression does occur in response to disability, rehabilitation teams tend to overestimate the incidence and intensity.[2]

Each treatment refusal or patient challenge must be examined and managed on an individual basis. The context from which the refusal arises and the personal and medical history of a patient may elucidate the specific factors motivating the patient's refusal of treatment and lead to a workable solution. The following rehabilitation cases illustrate some factors underlying treatment refusals.

Family Medical History Influences Treatment Refusal

The patient, a 47-year-old man, became a C-5 quadriplegic as a result of a motor vehicle accident. Early in his hospital stay, he required a tracheostomy. Five weeks after his injury, a severe pneumonia developed and the patient needed mechanical ventilation. He vehemently refused this intervention.

The staff first thought this decision reflected suicidal intent. Conversations with the patient and his family revealed that he had watched his terminally ill mother linger through a long hospital stay while on a ventilator and had vowed to avoid a similar situation. After the team clarified his medical status and explained that the likelihood of prolonged mechanical ventilation was slight, his fears were alleviated and he agreed to the intervention.

Prolonged Loss of Control Produces Pervasive Resistance to Care

The patient, a 17-year-old high school senior, was the victim of a "drive-by" shooting that resulted in a C-7 quadriplegia. The family characterized him as a diligent, hard-working young man who previously was not prone to rebellious behavior. His rehabilitation was delayed in part by his noncompliance. His intermittent refusal of nursing care after his first week in the hospital resulted in deteriorating pulmonary status with recurrent pneumonia and decubitus ulcers. He angrily refused nursing care procedures that were considered medically necessary. Because he was a minor, his family's wishes took precedence, and treatment was provided.

Numerous conversations with the patient revealed that he was generally frightened and traumatized by the loss of control of both his body and life. He responded well to empathic support and education. Choices were offered whenever possible regarding his care.

Incongruence of Patient-Team Goals and Values

The patient, a 70-year-old woman with a below-the-knee amputation due to peripheral vascular disease, was admitted for rehabilitation. The treating team thought that the goal of independent ambulation with prosthesis and a walker was reasonable. The patient, however, did not want to walk. She saw herself as an elderly woman who was able to afford the services of assisted care. She was content to live at a wheelchair level, and her family agreed with this plan. The staff was distressed by her unwillingness to challenge herself and adopt the goals that they had set for her. Despite the persuasive efforts of her therapists, the patient remained firm in her decision not to attempt walking again. Although the rehabilitation team had set certain goals, the patient neither shared these goals nor agreed to them on admission. She was discharged after ten days of rehabilitation, independent in wheelchair skills. It was necessary for the rehabilitation team to reflect on the need to respect differing goals and values.

Recommendations for Conflict Management

We have found that the following strategies help to keep patient-team care conflicts from erupting and can guide problem solving when conflicts arise:

- Patients should be involved in setting goals and planning treatment on admission. Treatment objectives should be discussed by the physician and patient, documented, and placed in the chart for update and reference. This contract may serve as the basis for education and discussion and helps to encourage a shared perspective and purpose.
- The rehabilitation team should develop guidelines regarding medically necessary care. Some aspects of treatment may be administered in a more flexible manner, enhancing patients' sense of control. For example, suctioning may be considered medically necessary, but attempts should be made to involve the patient in the scheduling of the procedure.
- Patients and families should have regular opportunities to express their needs, wishes, opinions, and fears regarding their care and treatment. Patients need time to voice concerns in private. Psychological services, family meetings, and updates from the team on patients' progress are necessary.
- Rehabilitation team members also need regular opportunities to discuss their concerns and ideas regarding the care of patients, as well as their professional role, demands, and responses to difficult situations. Patient care conferences rarely provide sufficient opportunity for open, frank expression of individual concerns. When patients challenge or refuse care, special meetings may be needed. Expert clinical supervision of care givers is vital to provide guidance and prevent job burnout.

Conclusion

It is not easy to deal with a patient who is refusing care. Health professionals may be frustrated by treatment refusals. It is important at all times to have open lines of communication with the patient, family, and treating team.[3] If a decision is made to override a patient's autonomy, this must be carefully examined to specify exactly which treatment is to be "forced," the rationale for this action, and the time course for this treatment. Throughout this process, the patient must be supported psychologically. Treatment refusal conflicts may be more agreeably resolved by careful adherence to the guidelines prescribed above, with the patient as an active vocal member of the team.

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Treating Families Coping With Disability
Doing No Harm

CAROL J. GILL, PhD, *Willowbrook, Illinois*

In our culture, disability is one of the most dreaded experiences a family can encounter. When a child is born, most families express concerns that are, in fact, questions about disability: Is the baby all right? Does she have all her fingers and toes? Public opinion regarding health issues suggests that disability has supplanted death as the worst thing that can happen (C. Page, "'Doctor Death' and His Grim Machine," *Chicago Tribune*, June 10, 1990, Sec 4, p 4). Even some "pro-life" groups now place the risk of disability alongside rape and incest as a legitimate basis for abortion (M. Senander, "Abortion as Birth Control: Prolifers Shouldn't Make Exceptions," *Minneapolis Star Tribune*, February 27, 1990, p 11A).

In this social context, it is not surprising that families are thrown into crisis when one of their members acquires or is born with a disability. Families experience profound grief, guilt, fear, and bewilderment.[1] They rely on physicians to guide them through the crisis and help them make sense of the disability.[2] But first, physicians themselves must make sense of it.

It is a challenge for health professionals to acquire the kind of knowledge and understanding of disability needed to be helpful. They are handicapped in this endeavor in several ways:

- Research on attitudes shows that physicians harbor many of the same narrow prejudices about disability that the general public does.[3]
- Medical training fails to prepare physicians for the unique medical status of many disabled persons.[4] Only a portion of disabilities are amenable to traditional medical management. Moreover, viewing disability through a medical model falsely enlarges the importance of physical issues in disability. Given sufficient time and resources, most disabled people make peace with their medical status. Their real problems, most insist, are not physical but social.[5]
- The professional literature fails to provide data relevant to understanding the complexities of living with a disability. Neither clinical studies nor anecdotal reports adequately illuminate disability issues.
- What clinicians know about disabled people is associated with pathologic disorder. They meet disabled persons seeking help with medical problems or those overwhelmed by new disabilities. They rarely get to know or learn from the larger community of people who have achieved a stable adjustment.

Despite these limitations, physicians can help families in crisis. As soon as possible after a disability occurs, the family should be encouraged to secure emotional support from relatives, friends, clergy, mental health professionals, or self-help advocates. Family members will still look to a physician for reassurance and interpretation of events, however. The family's concerns soon turn to questions of function: What will the disabled person be able to do normally, or at all? Will the person be useful, self-sufficient? Astute professionals realize such questions range far beyond objective physical data. They require interpreting the disability in a context of the cultural values of personal independence, quality of life, acceptable deviance, and social usefulness. This is the point at which a physician's message is crucial to the family's perceptions of disability and their ultimate adjustment.[6] A false step can harm the developing relationship between the disabled person and the family.

If physicians plan to help disabled persons and their families, they must seek enlightenment beyond traditional training. They must get to know disabled persons living in the real world and learn from them a broader perspective. Reading books and articles by disabled activists can provide a good introduction. Disability political organizations, peer advocacy groups, and independent-living centers staffed by disabled persons are important sources of information. Professionals who wish to be helpful must be willing to admit their own prejudices and gaps in knowledge and be prepared to refer families to other sources of guidance.

Of all the positive things physicians can do to help families cope with disability, two are imperative. First, they can help families understand that the medical aspect of disability is only the tip of the iceberg. Disabled persons and their loved ones must be encouraged to learn about the social aspects of disability; they need to appreciate the complexity, richness, and challenges of being disabled in a nondisabled world. Ultimately, they must learn about this to lessen the damaging effects of disability prejudice in family life. Second, physicians should urge disabled persons to establish connections with others with disabilities. While newly disabled persons may initially question or openly resist the need for this, positive peer experiences are an important component in developing self-regard and identity as a disabled person. Moreover, the disability community offers the best possible information about resources and tips for survival.

I once spoke to a woman whose daughter is a disabled professional with her own child and husband. She told me this story: One day, a few years following the illness that

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From the Chicago Institute of Disability Research, Willowbrook, Illinois.
Reprint requests to Carol J. Gill, PhD, 7223 S Kingery, Suite 225, Willowbrook, IL 60521.

resulted in her daughter's disability, the mother observed sadly that the anniversary date of the disability was approaching. To the mother's great surprise, her daughter responded by challenging her to start viewing the disability as a change that had brought many positive experiences into their lives. She then listed those experiences. After taking several days to assimilate her daughter's gentle rebuke, the mother remembers making a conscious resolution to expand her view of disability. Each year, since that day, she has sent her daughter a bouquet of flowers with a message that says, "Congratulations on the anniversary of your new life!"

When I tell this story to nondisabled persons, they often look confused or uncomfortable. Disabled persons, however, are profoundly touched. Many have been moved to tears, expressing their longing for "a mother like that."

All disabled persons deserve "families like that," families who love them completely, who appreciate both their difference from and their sameness to the rest of the family. Families deserve the benefits that come from learning about life through the experience of disabled loved ones. Although it is a weighty responsibility, physicians must come to terms with their key role in the adjustment of disabled people and their families. There is no neutral position. Medical professionals who fail to use their power for good—to encourage disabled people and their families to understand the social reality of disability—are contributing to a medical tradition that has done immeasurable harm. It is time for physicians to approach disability in a way that can help heal not merely bodies but lives.

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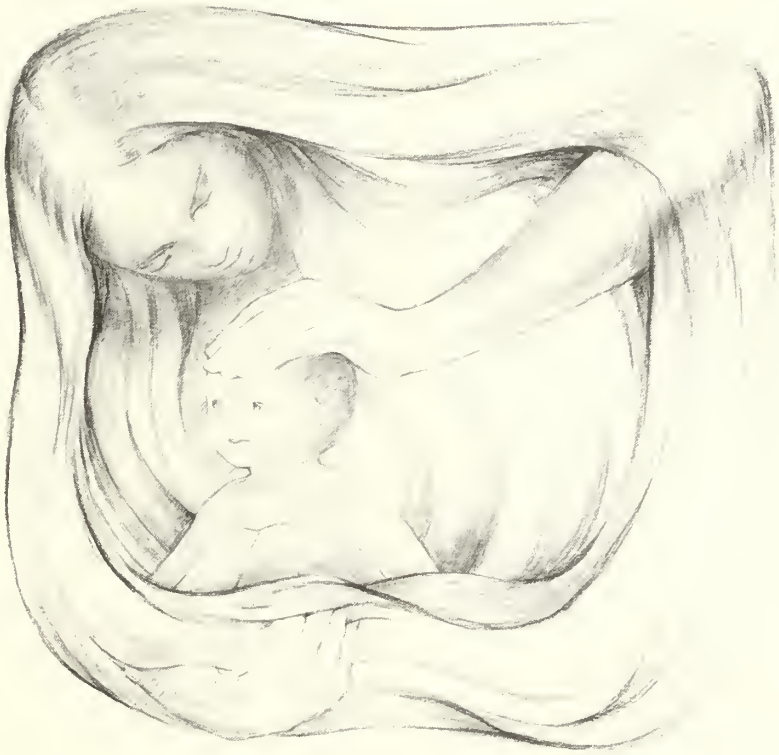

I feel that, deep in our cells, lie roots of the essence of giving and nurturing that starts at, or even before, our birth. The need to be able to both give and receive, a beautiful endless line (symbolized in the drawing by the mother's hair) follows us through life to its end. Often we feel deep satisfaction when we are able to be, at times, the spiritual donor, and, other times, the recipient. The best may be when we experience both at the same time. In medicine, we have the privilege of thousands of opportunities to experience the latter, and for this I am very grateful.

HARRIS MEISEL, MD
Santa Barbara, California
"GIVING"
32" × 32" charcoal drawing

Taking Rehab Home

NANCY BECKER KENNEDY, *Los Angeles, California*

It's funny what can happen when you volunteer in a rehab hospital. Pretty safe stuff, you might think. A way to keep a woman with quadriplegia at the C5-6 level, 18 years after the injury, off the streets. Not so. One master's degree, one divorce, three prestigious careers, and two modified vans later, I am in the second week of a trial and facing a possible jail sentence. For what? Trying to make sure that newly injured people get the same opportunities I had to return to the mainstream of life.

You may be asking, "What does all this have to do with being a doctor?" The answer is, if you are a physician, especially a specialist in rehabilitation, you must know that the patient who leaves your hospital with a disability is entering an oftentimes dangerous world of bureaucracy and budget cutting. In that milieu, they will attempt to continue the rehabilitation you all set out to achieve. When they leave, they may need you more than ever. Conscientious specialists in rehab medicine, a rare and precious kind of healer, know that to really complete the job, they have to be there to support their former patients years after they have left the cocoon of the rehabilitation facility.

To understand your challenge in making inpatient rehabilitation stick for outpatients, you must realize that the most enormous obstacle you and your soon-to-be-former patient will face when taking rehab home is MONEY. Most people with disabilities are forced into a cycle of poverty because the life of a severely disabled person is an expensive one. There are the costs of attendant services, durable medical equipment, large monthly pharmaceutical bills for medicine and supplies, modified homes and vans, and all the expenses incurred when persons can't economize because they can't cook, launder, pump gas, or do anything the self-serve way.

Unless your patients win an enormous personal injury settlement or can work in a profession that pays around $50,000 a year and can be performed by quadriplegics, they will be forced to rely to some extent on government-funded medical care. In this country, that care is provided through the welfare system, a program that is not famous for ushering people to independence. In fact, dealing with the system has literally frustrated some disabled people to death.

Every physician must be frustrated by Medicare or Medicaid, insensitively administered programs at best and deadly negligent at their worst (the latter more and more the case because of the erosion of the system by budget cutting in the past ten years). I am now standing trial with two other disabled activists because a disabled man was dying of bedsores and pneumonia because Medicare and Medi-Cal [California's Medicaid] refused to offer sufficient funding to replace the 17-year-old wheelchair that broke underneath him. The case of Rick Tauscher is a classic one of how this hostile milieu can undo all the good your efforts at rehabilitation achieved.

A mechanic before his injury that resulted in C-3 quadriplegia, Rick Tauscher was a rehab success story. Armed with a positive attitude, the willingness to work after his severe spinal cord injury, and enough pluck to supply a small town, Rick got up every morning and resumed an active life, supervising engine repairs in his garage. Okay, maybe he wasn't pulling down a lot of money, but he was being productive, getting around town, enjoying life, and could have even started making money, paying taxes, and giving back some of the benefits he was receiving due to the passage of a hard-won piece of legislation that began to remove some of disabled people's barriers to employment. But before the Social Security laws went into effect, in another part of the red-tape maze, Medicare and Medicaid were in the process of a malign neglect that would land Rick in worse condition than his original injury.

Here's how it happened. When Rick's wheelchair turned about 15 years old, it started getting rickety. His physical therapist ordered a replacement, while his brother spot welded it to get him by till the new one came. Unfortunately, years went by and no new wheelchair came. None was even on its way. And all because Rick had worked before his injury and was eligible for Medicare as well as Medicaid. Had Rick only been on welfare, Medi-Cal would have paid for his wheelchair. Unfortunately for Rick, *because* he had contributed to Social Security before his injury, he was in a classification that sent heads wagging back and forth mournfully in wheelchair stores all across the state. When the vendors handed back the prescription, the answer was always the same: "We can't do anything, you're a 'Medi-Medi.'"

For three years now, Rick has been literally bedridden by this "catch-22." Medicare, the primary insurer, would only pay a fraction of the real cost of a replacement electric wheelchair, and Medi-Cal would only pay 20% of what Medicare allowed. No wheelchair vendor was willing to give away a $14,000 wheelchair for $3,000. To make matters worse, because Rick was on Medi-Cal, even if he could miraculously raise the remaining $11,000, no store was allowed to take additional money from him. Now, the only way to appeal a Medicare decision is to purchase the wheelchair first, but because the vendor could not take any additional money, Rick could not purchase the chair and therefore had no way to begin the process of appeal. And so it went, around and around and ultimately nowhere.

(Kennedy NB. Taking rehab home. *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:626-628)

Nancy Becker Kennedy became quadriplegic after breaking her neck (C5-6) diving in 1972. Since then, she has returned to college for her bachelor of arts and a master's degree in broadcast journalism. She is an award-winning free-lance writer and producer for public television in Los Angeles.

Reprint requests to Nancy Becker Kennedy, 3961 Via Marisol, #233, Los Angeles, CA 90042.

While the question of whether Medicare was willing to pay too little or the vendor was asking far too much may have been a valid topic for debate, it was a moot point for Rick. Four bouts of pneumonia, two bronchoscopies, one operation for bedsores, and a case of multiple-resistance *Staphylococcus aureus* infection later, as a result of his three years in bed, Rick was caught in the middle and quietly dying of red tape.

My calls to congressional representatives proved fruitless. The "Medi-Medi" catch-22 had been known to them for years, and there was nothing anyone was willing to do to stop the machine from rolling over Rick. All the rehabilitation that returned him to a life of activity repairing engines in his garage was lost. The cherry on top is that it was costing taxpayers hundreds of thousands of dollars for the government to ruin Rick's health rather than make the $14,000 investment in his active life. As we marched with Rick to the governor's office, I heard a woman bystander say, "If he can't get a wheelchair, what am I paying my taxes for?"

As Rick's freedom became a memory, and his health deteriorated rapidly, I was running out of options. I enlisted the support of my friends in ADAPT, a disabled activists' organization dedicated to the advancement of the health, dignity, and full integration of people with disabilities. We engaged in nonviolent civil disobedience over the course of two months to call attention to the damage being done by cuts in government-funded medical care. We brought Rick out on a gurney to the governor's office to show him what a budget cut looked like and to ask for help for Rick. When none was offered, we staged sit-ins every day, got arrested, and refused to leave until we had a work order for Rick's chair and a resolution to the catch-22 that was affecting countless other "Medi-Medis" throughout the state.

There is a happy ending to this story. If my fellow activists and I are not sent to jail, it will be a total victory. Last October, the sit-in resulted in the filing and the eventual settlement of a class-action lawsuit that resulted in a court order for Rick's wheelchair and for all the other "Medi-Medi" patients throughout the state.

Unfortunately, the "Medi-Medi" catch-22 is just one of many life-endangering crises occurring in our state and throughout the country. Budget cutting to Medicaid and Medicare has resulted in physical harm to disabled people dependent on these government programs. As reimbursement rates fall well below market prices for doctor's visits, vital medicines, procedures, and orthotic devices, people get sicker, lose years off their lives, and function at lower levels. I have watched this deterioration to rehabilitation firsthand, as I have gone back month after month over the past ten years to counsel the newly injured.

Ironically, I first came to counsel new patients when I saw how active my life had become since my injury. With a wonderful array of support services—from excellent rehabilitation, attending a college with a fine disabled-students' program, and later the help of the US Department of Rehabilitation—I became a producer for public television and have gone on to enjoy many professional accomplishments. But I was lucky. I was always in the right place at the right time in terms of support services. I now live independently in my own home with an attendant and drive my own van purchased from my earnings. I am an example of how well rehabilitation works.

As I see this support system begin to crumble, the good news I come to tell newly injured patients gets a little harder to tell. I'll be going back to Northridge University's Institute for Living tomorrow. I will still tell patients how full their lives can be with a disability. But I don't think I'll tell them about the three years Rick has spent in bed or about my friend Sally who had to panhandle the money for antibiotics with a fever. And I won't tell them about Linda, a brilliant activist driven to the edge of despair when red tape and budget cutting kept her from getting medical care as basic as an air hose for her respirator.

What I learned early on—and what has become more obvious in the past ten years—is that to rehabilitate a disabled person, we must teach survival skills for an increasingly toxic health care environment. It is ironic that on the eve of the passage of our precious civil rights bill, the Americans With Disabilities Act of 1990, the safety nets and services that facilitate our independence are being cut out from under us. To stabilize your patient's bodies is no longer enough. If we want to rehabilitate patients and usher them from monetary dependence to a productive life, we must prepare them for the world outside and we must prepare the world outside for them.

To prepare patients for the world outside, physicians must know about the kind of world their patients are entering. To accomplish this, it is crucial to honor and utilize the skills of people who have lived successfully with their disabilities in the community. A new member should be added to all rehabilitation teams. In addition to the physician, nurse, physical therapist, occupational therapist, social worker, and psychologist, there must be an "independent living specialist." The independent living specialist should be someone who requires attendant and independent living services and has lived actively in the community, someone who can guide newly injured patients and their families through the treacherous terrain of red tape to get what they need. Patients and their families must be taught how to turn their new areas of dependency into a job for an attendant. They need to be shown how to advertise for and screen attendants to care for them in their homes and how to get homemaker allowances to pay for them. They need to know how to wrestle with the Social Security system and how not to trip trapdoors that drop vital services out from under them before their employment can adequately pay for their needs.

To prepare the world outside for rehabilitated patients, doctors can affect public policy, first, by learning from those living with their conditions what they need, and then by lending their prestige to the struggle for programs that promote productivity and health. If your patients will need help when they return home and there are no attendant services in your state, your voice is needed to bring this cost-efficient, life-enhancing alternative to those who could live outside institutions where many are inappropriately warehoused. Perhaps most critically, physicians must make themselves heard to fight against cuts in medical treatment by telling legislators what is needed to practice medicine instead of letting clerks at Medicaid and Medicare practice it for you. We all must do what we can to reform the current state of medical care in this country, the only industrialized nation besides South Africa that has no national health policy.

As money gets tighter nationally, a medical "lifeboat mentality" arises. There will be temptations to toss people and vital medical procedures overboard. Decisions as to which lives are more worth saving than others can lead to

serious moral and ethical violations. If medical services must be curtailed, if they are not cut equally for everyone, what are we taking part in?

I have seen rehabilitation work in my own life. I would like to see the choice for attendant services that enabled me to live independently and work extended to everyone who has a disability and needs help. I would like to see the day when people with disabilities are untied from welfare and able to receive the medical care they need and rehabilitation that ushers them from dependence to independence. I would like to see rehabilitation programs welcome the skills of people living actively with their disabilities as a treasured resource to assist patients back into the mainstream of life.

If physicians can see their former patients as valued allies, we can face this medical crisis together. We must get the message out that we are not about the right to die for the purpose of trimming down life to suit the budget. In the debate about the allocation of medical resources in this country, we must avoid the trap of choosing who should die a little earlier and who should get a little less medical care. As physicians, as healers, and as those who have healed, we must teach this nation that we are about life.

* * *

POSTSCRIPT: *Good news. Rick got his chair at the end of January. All Medi-Medis are now able to get wheelchairs. A judge allowed the "not guilty by reason of necessity" defense in our trial; the prosecutors saw they were licked and dropped the charges.*

CHAMPION OF THE WORLD

My wheelchair sparkled colors
in the New York sun
My horse at my side.
My hands tense,
fingers curled nervously
Weakened eyes groping and unaware.
Glory in a moment's breath,
Champion, or just another athlete.
Seconds to mount
I'm hoisted up to a throne of kings,
riding to a battle with no defeat.
The ring is dark to me, and foreign.
My walkie-talkie directs me smoothly.
My eyes set in blank distance.
My competitor is my own body,
the battle of illness against myself.
My back rests against the sky,
and I am free.
And when it is over,
my feet sink into my horse's sides,
and relax with reassurance.
I've waited a lifetime
for this moment.
I look into a faded, blurry crowd.
They call my name.
I am champion of the world.

MIKKO MAYEDA©
Ontario, California

Ms Mayeda is legally blind—she has light perception only. She also has left hemiparesis due to multiple sclerosis. When riding she uses a walkie-talkie to guide her through her maneuvers.

Rehabilitation—Women's Perspective

EDITOR'S NOTE: *Women and men have special needs in rehabilitation. Women's needs, however, have received far less attention in the scientific community and medical literature. This section, edited by Sandra Cole, PhD,* highlights some of the unique concerns of women who live with physical disabilities.*

*Director, Sexuality Training Center, Department of Physical Medicine and Rehabilitation, University Hospital, Ann Arbor, Michigan.

Protecting Reproductive Health and Choice

BARBARA FAYE WAXMAN
Los Angeles, California

DISABLED WOMEN in general do not have freedom of choice regarding their reproductive health or their future. Over the years, family planning and reproductive health services have largely been aimed at keeping disabled women from having children. In fact, well over three quarters of Americans view a woman's disability as an acceptable reason for her not to have children. The use and abuse of sterilization, abortion, and hormonal (Depo-Provera) therapy especially directed at developmentally disabled women have furthered this societal expectation. At the same time, many disabled women are unable to prevent a pregnancy they do not want. Such women characteristically undergo late abortions or must carry to term.

Although ignorance and prejudice about disabled women are deeply ingrained in our culture, health service providers must rise above these biased beliefs and acknowledge that disabled women and adolescent girls are sexually active more than ever before and are at risk for sexually transmitted diseases and unwanted pregnancies. In addition, they may need advice and assistance in planning wanted pregnancies. Disabled women are therefore requiring and demanding reproductive health services and reproductive choice.

What services are disabled women actually receiving? Beckman and colleagues reported that most participants received gynecologic and contraceptive services. This finding is contrary to anecdotal evidence, including my experience with providing such services, and other research results. This survey included only physically disabled women activists, who tend to be more aware of their rights to medical care and skilled in obtaining those services. Whether less-informed physically disabled women and women with hearing, visual, and developmental disabilities are receiving services is still largely unknown. Despite differences with other work, this study, as well as others, found that these same women did not feel the freedom to ask for, or adequately receive, information or education about their sexual and reproductive health.

Disabled women want and need physicians and other health care workers to be well trained in the medical and psychosocial aspects of their sexuality. Such education will ensure reproductive choice and will enable practitioners and disabled women to establish good communication in the decision-making process. Disabled women, because most are poor, also need more physicians and family planning clinics that accept Medicaid to pay for these services.

Disabled women know and understand their bodies and lives in elaborate ways. They are striving for self-determination in all aspects of their lives, particularly the aspect that has been most denied them—their sexual and reproductive freedom. When affordable and comprehensive reproductive health services finally become accessible to the disability community, disabled women will be able to exercise their most personal civil right.

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(Waxman BF: Protecting reproductive health and choice, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:629)

Ms Waxman is a student in the graduate school of Architecture and Urban Planning at the University of California, Los Angeles.

Reprint requests to Barbara F. Waxman, PO Box 127, 8883 Pico Blvd, Los Angeles, CA 90035.

Affirming Adolescent Women's Sexuality

HARILYN ROUSSO, CSW
New York, New York

MANY ADOLESCENT WOMEN with physical or sensory disabilities have less active social and sexual lives than their nondisabled counterparts. They tend to socialize with peers less often and have their first date, kiss, sexual encounter, and steady partner at a later age. These young women are no less interested in the social arena than those without disabilities, but they face limited opportunities and myriad obstacles

(Rousso H: Affirming adolescent women's sexuality, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:629-630)

Ms Rousso is Director of Disabilities Unlimited Psychotherapy and Consultative Services, New York, and a member of the New York City Human Rights Commission.

Reprint requests to Harilyn Rousso, CSW, 3 E 10th St, Apt 4B, New York, NY 10003.

reflecting the pervasive societal myth that women with disabilities cannot or should not be sexual.

Young women with disabilities pay a high price for such exclusion. Blos and others have described how involvement in a range of social and sexual activities during adolescence eases the completion of a variety of developmental tasks, including separating from the family, developing social skills, exploring budding sexuality, and establishing the capacity for intimacy. In addition, the traditional and still widely held measure of a woman's success in our culture is her capacity to attract and keep a man. For adolescent women, therefore, the flurry of social activities, particularly those of a heterosexual nature, is seen as a confirmation of womanhood, and the absence of such activities becomes a sign of failure. Because our culture devalues disabled women and questions their womanhood by virtue of their disability, for adolescent women with disabilities, the lack of social success may be one more reason to not feel like "true" women.

Some young women with disabilities do have fulfilling social lives, however. What enables them to succeed? As in other areas of adolescent achievement, a significant factor may be parental expectations. According to my 1988 study, when parents expected their disabled daughter to be socially active, she was more likely to be so. The young woman set positive expectations for herself and called on her parents to help her overcome some of the hurdles. For such parents, their daughter's disability did not compromise her womanliness or sexual potential.

Only a small percentage of the parents in this study had positive expectations for their daughter's social future. Most had serious doubts about the ability of their teenager to find romantic partners, and their daughter got the message. Some of the teen women succeeded despite their parents, often relying on another relative or a friend to affirm their sexuality. Most of the adolescents, however, were not so fortunate. Restricted by their parents' and their community's limited expectations, they did not begin exploring their sexuality until well into adulthood.

Physicians and other professionals working with adolescent women with disabilities and their families can play an important role in helping these young women to enter the social arena. They can help parents develop more positive attitudes or, failing that, can serve as a counterbalance to parental pessimism. Both parents and daughters need to hear that women with disabilities can find partners, enjoy sex, and have children, although such accomplishments may require an assertive, creative stance because of societal prejudices. Encouraging contact with successful disabled women in the community who serve as role models can also foster positive expectations.

Because of taboos, disabled young women may be reluctant to ask questions about sex. Professionals can break the "conspiracy of silence" by raising sexual issues themselves. It is often useful to provide specific information on how a young woman's disability will affect her sexual functioning and fertility. It is distressing how little many disabled teenaged women know about their disabilities and their bodies in general; as a result, misconceptions abound. Although parents and professionals are sometimes reluctant to tell disabled youth "the truth" about their disabilities, in actuality, facts are much less frightening than fantasies created by a lack of knowledge.

While many disabled teenaged women have less satisfying social lives than their nondisabled sisters, this is not the inevitable consequence of disability. Physicians can actively encourage these young women to take on the social scene or, through their silence, they can become part of the problem.

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Reclaiming Sexual Self-Esteem—Peer Counseling for Disabled Women

MARSHA SAXTON, MS
Boston, Massachusetts

"CAN DISABLED PEOPLE have sex?" This is one of the most frequently asked questions in disability awareness workshops. We live in a society where issues of sexuality and disability are still taboo. It is often assumed that disabled people are asexual. It is no wonder, then, that people who become newly disabled, or those who grew up with a disability, may have difficulty handling the feelings and negotiating the logistics of sexual relationships.

Stereotypes about disability and sexuality hit women in particular ways: It is assumed that women must be attractive, as defined by cultural norms, to find love. It is assumed that orgasm is necessary for "real" sex. And "safe" heterosexual sex means intercourse. Even with the precautions of safe sex, the media's message is that sex should not be discussed or planned but must be spontaneous. Such notions contribute to a sense of failure for disabled women.

Physicians and other health professionals are not immune to stereotypes. They may project a notion of falling short of normalcy onto their disabled patients. As in the larger culture, there is resistance to discussing sex. An informal survey of rehabilitation counselors revealed that although about 80% surveyed were willing to discuss issues of sexuality with their clients, only 16% actually had.

Persons with severe disability are considerably underserved by mental health professionals because of inadequate training, attitudinal barriers and the inaccessibility of programs. This is particularly true regarding sexual issues. In my organization serving disabled women, we observe exam-

(Saxton M: Reclaiming sexual self-esteem—Peer counseling for disabled women, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:630-631)

Ms Saxton is Executive Director of the Project on Women and Disability in Boston. She is a board member of the Boston Women's Health Book Collective and coeditor, with Florence Howe, of *With Wings, An Anthology of Literature By and About Women With Disabilities*, published by Feminist Press, New York, NY, 1987.

Reprint requests to Marsha Saxton, MS, Office of Handicapped Affairs, 1 Ashburn Pl, Rm 1305, Boston, MA 02108.

ples of overreferral to psychiatry for sexual problems (it is assumed that where there is a sexual problem, it must be related to the person's disability) or the opposite—advice to "adjust to your disability," meaning, "accept that sexual relationships are impossible."

Peer counseling is particularly useful regarding sexuality. Where pamphlets and educational videos offered by a professional may seem impersonal or remote, encouragement from a peer—"I know you can do it, because I can"—is extremely helpful. A peer counselor can provide information gained from real experience, inspire confidence, offer unimagined options, and stimulate a move toward creativity and experimentation.

In our organization, peer counseling groups on disabled women's sexuality illuminate the power of peer counseling. In a 12-week evening group, we focus each week on a selected topic (menstruation, birth control, pregnancy, childbirth, sexual intimacy, alternatives to traditional sexual positions, body image issues for disabled women) but allow each participant, during her turn in the group, to choose the feelings or issues most in need of attention for her.

The groups include people of different disability types, races, ages, and levels of education. This diversity works well to offer the widest view of what "normal" sexuality is supposed to be. During the meetings there are lots of laughter, considerable embarrassment, some tears, and a great deal of appreciation for each other's openness and risk taking in sharing feelings.

At the end of a 12-week group, most participants indicate, in tones of relief or surprise, their realization that sexuality in the context of a disability need not be viewed primarily as a lessening of function or intimacy but can become an opportunity for creativity and enhanced communication with partners. It is possible not only to continue sexual intimacy with a disability, but sometimes disability may force a person to move beyond rigid cultural notions of prescribed behaviors and options and seek human connection in new ways.

The Independent Living Movement needs physicians who will encourage peer groups and peer helping, who will know what peer programs are available and refer their patients or, where appropriate, encourage them to initiate their own groups.

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DREAMS OF FREEDOM

I hate the dependence I have on you. Oh, I try to accept and live the ever-present fact that without you I would essentially go nowhere, but the gnawing feelings of not quite being a whole person keep sweeping through my self confidence. You are so important in my daily life that I tend to overlook your outward ugliness and rely on you to support me and help me accomplish things that without you might have been impossible.

Do you know the embarrassment I feel deep inside when we are seen out in public together and people stare at you and at me with you? If I could just gain my independence and meet people on my own without you constantly being there between us, like a wall separating me from living my own life to its fullest.

My dreams are full of freedom. I'm running in a big open field with my friends, playing tag, feeling the cool green grass caressing my body as I tumble down a hill. But when I awake again I am thrown back into your dream-shattering reality, back to being confined and stifled by you.

I despise you and everything you stand for, demanding my dependence, making me appear different from the accepted norm and causing me to question intentions in fear that pity is lurking nearby. Yes I loathe the sight of you because together we become a girl in her wheelchair!

ROBYN OLSON©
Claremont, California

Robyn Olson became completely quadriplegic and blind in the last few years from juvenile rheumatoid arthritis and multiple sclerosis. She also received a degree in social work and is very active in helping other disabled persons.

Rehabilitation—An International Perspective

EDITOR'S NOTE: *The international community has perspective and experience that will freshen our approaches to rehabilitation. Martin Grabois, MD*, editor of this special section, has gathered articles written by experts from other countries. The intention is to stimulate thought, discussion, and action—and to broaden horizons.*

*Chair, Department of Physical Medicine, Baylor College of Medicine, Houston, Texas, and President, International Rehabilitation Medical Association.

Rehabilitation in the Philippines

TYRONE M. REYES, MD
Manila, Republic of the Philippines

THERE ARE 500 million disabled persons in the world, and estimates are that there will be 100 million more by the year 2000. Of these, 80% live in developing countries. Of the 146 million children with disability today, 88 million are in Asia. There can be no question, therefore, of the magnitude of this problem in the developing countries of the world—especially those in Asia.

This escalating demand for rehabilitative care is compounded by a shortage of trained rehabilitation personnel—particularly physicians—who can provide medical rehabilitation services.

In the early 1970s, before the start of the Regional Training Program at the Santo Tomas University Hospital in Manila, these problems were identified:

- A lack of physiatrists practicing in the Philippines—there were then only 10 physiatrists in a country with 4 million disabled persons.
- A "brain drain" of physiatrists—many Filipino physicians who trained abroad, especially in the United States, never returned to the Philippines. There were more Filipino physiatrists practicing in the United States than in the Philippines.
- A maldistribution of physiatrists—All the rehabilitation physicians were then practicing in Manila; none were in the provinces.
- The practicing physiatrists were too "Western." Their practice reflected their training in more economically advanced countries of the world with a different psychosocial background from where they would be practicing.

Howard Rusk, MD, mobilized the resources of the World Rehabilitation Fund to assist in organizing a program meant to train physiatrists initially for the Philippines—The Manila Program. The program was university-based, with good academic support from its medical school. The primary objective was to produce quality trainees who would be the future trainers. Training was done in the Philippines rather than abroad. Because graduates of the program would have responsibilities other than patient care, training and experience in teaching, research, administration, and public information were included. The program emphasized local diseases and conditions commonly seen and treated. It also considered native social and psychological values.

In 1977, three years after its launching, the program expanded to include the training of physicians from Indonesia, a country with a population of 150 million and not one physiatrist. This was done to produce the core trainers for several education centers in this adopted Asian country so that they could also begin an in-country training approach.

The selection criteria for trainees in the program were as follows:

- 35 years of age or younger;
- Proficient in the English language;
- At least a year of training in a related clinical field;
- Passing of a preresidency examination given by University Hospital and a 3-month preresidency clinical evaluation; and
- An assured place in an institution or hospital outside Manila, as certified by the proper hospital authorities.

The program has proved successful: 37 physiatrists—25 Filipinos and 12 Indonesians—graduated from the program from June of 1974 to May of 1990. All were given positions in various hospitals in different parts of the Philippines and Indonesia. Practically all major cities and regions in the Philippines now have been covered by the program. In Indonesia, at least three physiatrists have been assigned to the three in-country training centers in Jakarta, Surabaya, and Bandung. Of the 37 graduates, 35 have stayed in their originally assigned places.

Better success in the program was achieved when these factors were considered:

- The candidates came from the locality where they were going to practice. The advantages included continued family support, familiarity with local customs, and ability to speak the local dialect.
- The sponsoring hospital from the same locality requested the training of candidates, with a promise of taking them into its medical staff and supporting their practice upon the completion of training.
- Women were more likely to stay in practice in the locality assigned than were men.
- Necessary equipment was provided, especially to graduates practicing in rural areas.
- Patients were referred by the hospital staff. The reality is that financial viability plays an important part in successful seeding of candidates.
- There was continued moral support from the staff of the mother program. This included regular communication, networking of patients, and continuous intellectual stimulation by sending journals and articles and encouraging attendance of postgraduate courses.
- The graduates were able to work in more than one hospital in the locality. They would usually prefer to use a private hospital for private practice as a base and also work as a consultant in a government hospital that gave them a basic stipend.

(Reyes TM: Rehabilitation in the Philippines, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:632-633)

From the Division of Rehabilitation Medicine, Santo Tomas University Hospital, Manila, Republic of the Philippines.

Reprints not available.

Though much has already been accomplished, much more needs to be done. We now have more than 40 board-certified physiatrists working in the country. After we successfully concluded the Indonesian program, we started anew by adopting another Asian country—China. We hope that this program, using realistic approaches appropriate to the state of development of the countries concerned, may be replicated in other developing countries of the world.

Rehabilitation in China

DAHONG ZHUO, MD
Guangzhou, People's Republic of China

SINCE THE EARLY 1980s, rehabilitation medicine has developed rapidly as a medical specialty in China. Western techniques of medical rehabilitation have had a strong influence on treating physically disabling diseases and injuries in Chinese rehabilitation centers. With the influence of the cultural and social background and the heritage of traditional Chinese medicine, the practice and technique of medical rehabilitation in China bear some unique characteristics.

Priorities of Rehabilitation Programs

Because cerebrovascular accident is common, with an incidence of 280 to 480 per 100,000 persons, stroke rehabilitation is the major program in most medical rehabilitation institutions in China. Rehabilitation for low back pain is almost equally popular. Rehabilitation programs for geriatric diseases are offered in many rehabilitative sanatoria, especially for mild coronary heart disease, emphysema, and degenerative arthritis. In recent years, orthopedic rehabilitation by surgical procedure and functional training for late sequelae of poliomyelitis have been conducted throughout China.

Integrative Approach With Chinese and Western Methods

The traditional Chinese methods are widely used in Chinese rehabilitation institutions, along with the Western methods. Depending on each case, traditional Chinese medicine is used alone or in combination with Western methods.

Traditional Chinese physiotherapeutic methods used in physical rehabilitation include acupuncture/moxibustion, Chinese manipulation and massage, Tai Chi and other traditional therapeutic exercises, and Chi Kung (Qigong), a kind of meditation and relaxation therapy. Traditional Chinese arts and crafts and Chinese calligraphy are used as occupational therapy. Herbal medicine plays an important role in both physical and mental rehabilitation. A wide variety of conditions respond well to traditional Chinese medicine, such as hemiplegia and other forms of paralysis, chronic pain, musculoskeletal disorders and arthritis, soft tissue injuries, and psychosomatic diseases.

Notable progress has been made in recent years in combining the traditional methods with modern technology. The development of physiotherapy on the acupressure point is an example. It integrates Chinese Jing-Luo theory with modern physical medicine. Common modalities are electropuncture, ultrasound-puncture, microwave-puncture, laser acupuncture, and ultraviolet irradiation on acupressure points. The advantage is a safer and more accurate control of dosage of stimulation with diversified stimulant agents.

Community-based Rehabilitation

In 1986 China started her project in pioneering community-based rehabilitation. This new approach to rehabilitation service soon spread to over six provinces and four major cities. Because the government is taking the initiative, community-based rehabilitation should keep growing both in the number of pilot sites and in the quality of the field work.

Because China is a vast country, with 80% of the population living in rural areas, institution-based rehabilitation cannot meet the needs of disabled persons. Community-based programs are the only solution to the problem of inaccessibility of rehabilitation services. These pilot projects follow the World Health Organization model as described in the manual, "Training Disabled People in the Community." There are, however, distinct features in the Chinese approach:

- Programs are sponsored, organized, and supervised by the government through the sectors of Public Health and of Civil Affairs and Welfare;
- Programs use the personnel network of primary health care in the community, supplemented by volunteer community workers;
- Psychiatric rehabilitation is usually covered in the program;
- Home-based functional training is supplemented by training in a community-based rehabilitation administration;
- Programs use simple and useful methods as well as Chinese traditional methods.

(Zhuo D: Rehabilitation in China, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:633)

From the Department of Rehabilitation Medicine, Sun Yat-sen University of Medical Sciences, Guangzhou, People's Republic of China.

Reprints not available.

Rehabilitation in Mexico

HENRY ADAMS, PhD
San Miguel de Allende
Guanajuato, Mexico

AN INDEPENDENT living center for working age adults was established in Mexico in 1989. A retired rehabilitation advocate and administrator from California, Robert Wolfe, discovered three paraplegic men living in San Miguel de Allende, a colonial town in the state of Guanajuato, 160 miles north of Mexico City. Although the town had some excellent services for disabled children, there were none for adults. The three men knew of other physically challenged adults living in the town and others isolated in the nearby ranches. In the late 1970s Wolfe had a hand in securing start-up funding and establishing policies for California's 24 independent living centers. He had observed the Berkeley, California, self-help service delivery system and knew that it worked. These men decided to form a self-help group based on the Berkeley model. The new group in San Miguel was established as a nonprofit corporation and called itself "El Centro de Independencia."

El Centro now has grown to include 30 severely disabled

(Adams H: Rehabilitation in Mexico, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:633-634)

From El Centro de Independencia, San Miguel de Allende, Guanajuato, Mexico.

Reprints not available.

Mexican adults and is adding a new member on the average of every two weeks. The Mexican model as established in San Miguel de Allende, a community of 90,000 persons, includes the traditional services of peer counseling, independent living skills training, advocacy, information and referral, and outreach, but in the absence of a rehabilitation hospital, vocational rehabilitation workshops, and other resources, El Centro set about filling other gaps in services. First, a liaison was created with the town's quality care hospital, Unión Medica, which is affiliated with the School of Medicine of the University of California, San Diego. Members of El Centro receive routine, specialized, and emergency care through this facility. Next, El Centro attracted the volunteer services of a retired occupational therapist from the United States and a physical therapist with extensive experience in medical facilities in Mexico City. A Mexican male nurse was hired on a full-time basis to provide service in the home, particularly to members who are paralyzed. A group exercise program was started. Hydrotherapy is available at a nearby hot springs resort. Group psychological services were begun with a volunteer Mexican psychologist.

Transportation—a new pickup truck—was obtained when the group received proceeds from the national lottery. The group also successfully advocated for lottery funds to construct workshops. With start-up help from the community, El Centro equipped a jewelry-making workshop, began a job placement service, formed a wheelchair basketball team, secured donated rental housing, and purchased wheelchairs and wheelchair parts. A program of social activities was established early in the formation of the program.

El Centro plans to start a wheelchair manufacturing and sales business. Other small businesses being planned are wearable art, ceramics, garment making, and bicycle repair.

El Centro is entirely composed of adult Mexicans who are challenged by severe disabilities. A support group, "Los Amigos," open to all interested persons, helps with fundraising and public relations.

El Centro is encouraging other groups of adult disabled Mexicans to replicate the San Miguel model.

Rehabilitation in Great Britain

A. K. CLARKE, FRCP
Bath, Avon, Great Britain

GREAT BRITAIN probably is unique in the developed world in that the specialty of rehabilitation medicine is just becoming recognised. In many respects this is an accident of history. When the various groups of spa doctors and others using physical methods of treatment came together between the First and Second World Wars, they designated themselves consultants in physical medicine. With the passage of time, it became clear that most patients they were treating were suffering from rheumatic diseases, and the specialty of rheumatology emerged. This contrasts with most other countries where rheumatology arose from internal medicine. Most rheumatologists, especially outside the main teaching centres, also ran the rehabilitation services. Other features that delayed the emergence of a rehabilitation specialty were the comparative rarity of spinal injury in Britain, strong family practice, amputation services being run by a government service entirely separate from the National Health Service, and the well developed, if underrated, professions of physiotherapy and occupational therapy.

One consequence has been that rheumatologic rehabilitation has become highly developed. A recent government survey has shown that not only do the rheumatic diseases form the largest group of disabling conditions in Britain, but they also represent the largest number of severely disabled people in the country at this time. There are only around 350 full-time rheumatologists in Britain—for a population of 56 million—but they are well spread throughout the country, uniformly trained and experienced, and tend to offer good rehabilitation for their patients.

A number of people are involved in the care of patients. A rheumatologist will establish the diagnosis, make an attempt at predicting outcome, and initiate drug, physical, and, if appropriate, surgical treatment. A physiotherapist will provide assessment of disability and the requirements for treatment, education of the patient, and certain physical modalities. Of these the most important is exercise, which has been shown to be of benefit in a range of conditions.

The occupational therapist's responsibilities include hand assessment, activities of daily living, wheelchair assessment, and home visiting. Help will be given with household and personal chores and with improving the workplace, often with the provision of technical equipment. Joint protection is an important educational topic. Splint-making may be done by a physiotherapist, occupational therapist, or an orthotist. A social worker provides advice on financial matters, assists with re-housing, and can provide a counseling service for family and other personal problems. Apart from making simple splints, orthotists have a special role in rheumatology in the provision of footwear. Painful feet are a major problem in diseases such as rheumatoid arthritis. Rheumatology nurses also have special skills, including education and help with preventing and treating skin ulceration, which is common in the rheumatic diseases.

There is a strong tradition in Britain to provide support for unemployed people, including assessment and placement. This applies to disabled people as well as able-bodied ones. Disablement resettlement officers are the important link and are found in every major town and city. They are responsible for a wide range of services provided by the government to help people with work-related problems because of ill health or disability. Another strong tradition is the wide range of self-help and charitable groups working in Britain. For rheumatic patients, they range from Arthritis Care and the National Ankylosing Spondylitis Society, which are mainly concerned with patient welfare, to the Arthritis and Rheumatism Council, whose main job is to fund research and education into all aspects of these crippling diseases.

Rheumatic patients in Britain are better off than many of their disabled peers, most notably those with neurologic disease. Rheumatologists in Britain understand and practice rehabilitation as part of total patient care. They have built excellent teams to assist them. The need now is to extend that practice to all rheumatic sufferers and more widely to all disabled and handicapped people by establishing a proper specialty of rehabilitation medicine in Britain.

(Clarke AK: Rehabilitation in Great Britain, *In* Rehabilitation Medicine—Adding Life to Years [Special Issue]. West J Med 1991 May; 154:634)

From the Royal National Hospital for Rheumatic Diseases, Bath, Avon, Great Britain.

Reprints not available.

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(Continued from Page 506)

RADIOLOGY

July 18-21—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, Coronado. Thurs-Sun. 19.5 hrs. $400. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-24—**Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Wed. 14 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-27—**5th Annual MRI Symposium Including: Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Sat. 31 hrs. $695. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 25-28—**5th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 18 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

August 4-8—**Napa Valley Imaging Update-MRI 1991.** UCD at Silverado Country Club, Napa. Sun-Thurs. 17 hrs. $465. Contact: UCD.

August 12-16—**Radiology for Clinicians.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 11-13—**The 7th Annual Sonography Update Conference and Exhibit.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 14-15—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 23-26—**Applied Ultrasound: Accent on Doppler.** University of Alabama at Birmingham at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 25-28—**Diagnosis of Musculoskeletal Disorders: State of the Art.** International Skeletal Society at Hotel del Coronado, San Diego. Wed-Sat. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 17-20—**1991 Annual Scientific Meeting.** Western Neuroradiological Society at Ritz Carlton Resort, Laguna Niguel. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-27—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $225. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 28-November 1—**Sixteenth Annual Postgradnate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 28.25 hrs. $550. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

May 16-18—**What's New in Rehabilitation?** Memorial/UCI Center for Health Education at Queen Mary Hotel, Long Beach. Thurs-Sat. 9 hrs. Contact: UCI.

SURGERY

May 15-19—**13th Annual Wound Management Workshop: May.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $435. Contact: UCSD.

June 8-9—**Laser Assisted Percutaneous Diskectomy.** Memorial/UCI Center for Health Education. Sat-Sun. Contact: UCI.

October 10-13—**Wound Management Workshop: October.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 18 hrs. $435. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

GENERAL/MULTIDISCIPLINARY

May 18—**Nutrition and Health: New Thoughts, New Connections.** UCLA Extension at UCLA. Sat. Contact: John G. Watson, (213) 825-1901.

May 23—**AIDS Update for Primary Care: Early Detection for Early Intervention.** Alta Bates-Herrick Hospital at Hospital Auditorium. Thurs. 7 hrs. $125. Contact: Mary Grim, (415) 540-1420.

June 28-30—**4th Annual Conference for the Medical Office Laboratory.** San Diego State University at Red Lion, San Diego. Fri-Sun. 18 hrs. $400. Contact: Anne Wright, (619) 594-6255.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 7-8—**Fourth Annual Perinatal Summer in the Mountains Conference.** Children's Hospital of Denver at Glenwood Springs. Fri-Sat. Contact: Christine Sievers, (303) 861-6413.

June 25-27—**Community Health Traineeship.** Children's Hospital, Denver. Tues-Thurs. Contact: Christine Sievers, (303) 861-6413.

June 28-29—**Billings Perinatal Conference.** Children's Hospital of Denver at Billings, Montana. Fri-Sat. Contact: Christine Sievers, (303) 861-6413.

July 11—**Cultural Considerations in Perinatal Nursing.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

July 25-27—**Preparing for Reform—Proposals, Assumptions and Implications for Financing American Health Care—11th Annual Montgomery Dorsey Symposium.** Presbyterian/St. Luke's Community Foundation at Vail. Thurs-Sat. Contact: Mary Pettigrew, (303) 322-3515.

August 4-8—**34th Annual Pediatric Program.** University of Colorado School of Medicine, Children's Hospital, and the Colorado Chapter of the American Academy of Pediatrics at the Given Institute, Aspen. Sun-Thurs. Contact: Bobbi Rubingh, 1 (800) 882-9153 or (303) 270-5196.

August 5-9—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

August 8—**Basic and Advanced Fetal Heart Rate Monitoring.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

September 5, 12, 19, 26—**Comprehensive Perinatal Nursing Course.** University of Colorado Health Sciences Center. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

September 27-28—**Montrose Fall Clinics for Physicians.** Montrose Memorial Hospital, Montrose. Fri-Sat. Contact: Kathy Holman, (303) 240-7397.

October 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 7-10—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 14—**Pre-term Infant Feeding Conference.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

November 22-23—**Colorado Springs Perinatal Conference.** Children's Hospital of Denver at Colorado Springs. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

December 2-6—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO (303) 270-5195.

IDAHO

July 25-27—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

(Continued on Page 640)

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(Continued from Page 638)

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

June 8—**Transfusion Medicine: What's New in 1991.** Sheraton Old Town Hotel, Albuquerque. Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

August 5-9—**Body Imaging: Ultrasound, CT, MR, Nuclear Medicine.** El Dorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

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AHA	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102 (801) 322-5601.
CH	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501 (801) 637-4800.
HCH	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744
ITS	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105 (801) 484-4456.
LDSH	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924
OSS	Ogden Surgical Society, PO Box 9311, Ogden 84409
PVH	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUMC	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664
VAMC	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148 (801) 582-1565.
VVMC	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587
WRI	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400

May 17—**Infectious Disease Update** (Sponsor: UUMC). Fri. Skaggs Hall Auditorium, University of Utah, Salt Lake City. Contact: (801) 581-8664.

May 30-31—**Communications Disorders** (Sponsor: UUMC). Thurs-Fri. Snowbird. Contact: (801) 581-8664.

June 9-11—**Interactive Video in Health Education—'Slice of Life'** (Sponsor: UUMC). Sun-Tues. University of Utah, Salt Lake City. Contact: (801) 581-8664.

June 17-21—**University of Utah School on Alcoholism and Other Drug Dependencies** (Sponsor: UUMC). Mon-Fri. University of Utah, Salt Lake City. Contact: (801) 581-8664.

July 8-13—**Update in Internal Medicine: Focus on Ambulatory Care Medicine** (Sponsor: UUMC). Sat-Thurs. Snowbird. Contact: (801) 581-8664.

July 12-14—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

September 27-29—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUMC). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 31—**Office Gynecology—1991.** Tacoma. Fri. Contact: PCMS.

June 1—**Substance Abuse.** Seattle. Sat. Contact: U/W.

June 7-8—**Topics in General Medicine.** Seattle. Fri-Sat. Contact: VMMC.

June 15—**Horizons in Urology.** Seattle. Sat. Contact: U/W.

June 24-25—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: VMMC, (206) 627-7137.

July 26-28—**Seafair XII: Regional Anesthesia.** Seattle. Fri-Sun. Contact: VMMC.

August 9-11—**International Conference on Pancreatic Cancer.** Seattle. Fri-Sun. Contact: VMMC.

September 12-13—**Resolving the Ethical Dilemmas in Animal Protocol Review.** Seattle. Thur-Fri. Contact: U/W.

September 26—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

December 6-7—**Urology.** Seattle. Fri-Sat. Contact: (206) 441-9762.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104 (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121 (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111 (206) 223-6898

WYOMING

June 13-15—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413. ◆

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Please see adjacent page for brief summary of prescribing information.

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Upjohn | DERMATOLOGY DIVISION

Rogaine® Rx
TOPICAL SOLUTION minoxidil 2%

INDICATIONS AND USAGE
Male pattern baldness (alopecia androgenetica) of the vertex of the scalp. No effect has been seen on frontal baldness. At least four months of treatment are generally required before evidence of hair growth can be expected, further growth continues through one year. The new growth is not permanent, cessation of treatment will lead to its loss in a few months.

CONTRAINDICATIONS
Hypersensitivity to minoxidil, propylene glycol or ethanol.

WARNINGS
1. *Need for normal scalp.* Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.
2. *Potential adverse effects.* Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect.
Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):
—salt and water retention, generalized and local edema
—pericardial effusion, pericarditis, tamponade
—tachycardia
—increased incidence of angina or new onset of angina
Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.
Potential patients should have a history and physical, should be advised of potential risks and a risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious. Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects.

PRECAUTIONS
General Precautions. Monitor patients one month after starting ROGAINE and at least every six months afterward. Discontinue ROGAINE if systemic effects occur. The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.
Avoid inhaling the spray.
Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption. ROGAINE is for topical use only. Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.
Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption.
Patient Information. A patient information leaflet is included with each package and in the full product information.
Drug Interactions. No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.
Carcinogenesis, Mutagenesis and Impairment of Fertility. No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice. In rats, there was a dose-dependent reduction in conception rate.
Pregnancy Category C. ROGAINE should not be used by pregnant women.
Labor and Delivery. The effects are not known.
Nursing Mothers. ROGAINE should not be administered.
Pediatric Use. Safety and effectiveness have not been established under age 18.

ADVERSE REACTIONS
ROGAINE was used by 3510 patients in placebo-controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.
Respiratory (bronchitis, upper respiratory infection, sinusitis) 5.95%. **Dermatologic** (irritant or allergic contact dermatitis) 5.27%. **Gastrointestinal** (diarrhea, nausea, vomiting) 3.42%. **Neurology** (headache, dizziness, faintness, light-headedness) 2.56%. **Musculoskeletal** (fractures, back pain, tendinitis) 2.17%. **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1.28%. **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1.03%. **Special Senses** (conjunctivitis, ear infections, vertigo) 0.94%. **Metabolic-Nutritional** (edema, weight gain) 0.60%. **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0.46%. **Genital Tract** (prostatitis, epididymitis) 0.46%. **Psychiatric** (anxiety, depression, fatigue) 0.28%. **Hematology** (lymphadenopathy, thrombocytopenia) 0.23%. **Endocrine** 0.09%.
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions. Additional events reported since marketing include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia.

DOSAGE AND ADMINISTRATION
Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily. Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards.

HOW SUPPLIED
60 mL bottle with multiple applicators NDC 0009-3367-05
Caution: Federal law prohibits dispensing without a prescription.

B-1-S

Upjohn DERMATOLOGY DIVISION

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Kalamazoo, MI 49001 USA

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YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

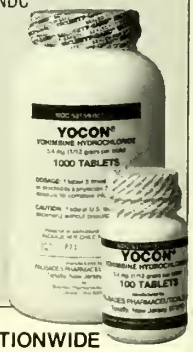
Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.



References:
1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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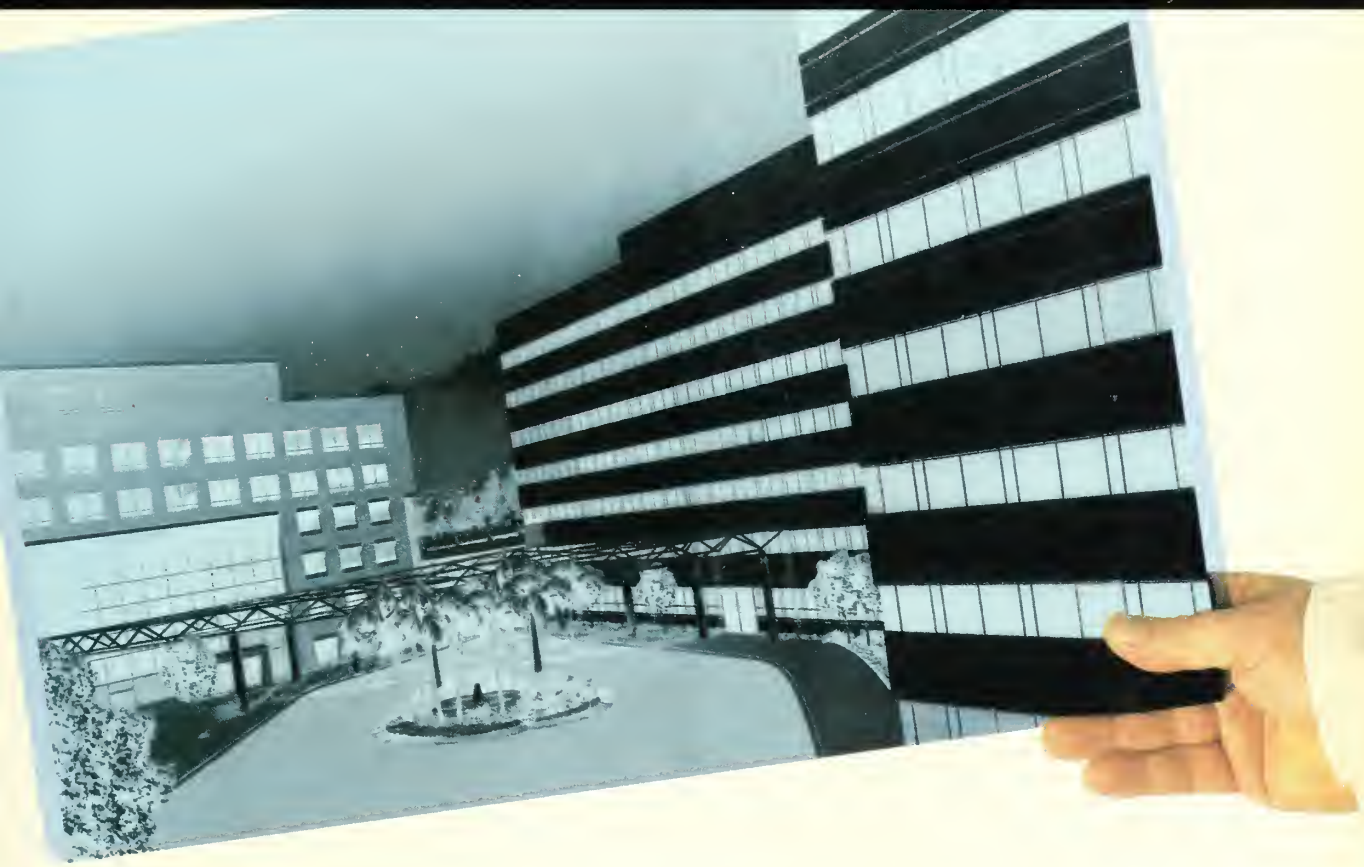

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KETCHIKAN, ALASKA. University of Washington-affiliated Family Practice seeking BC Family Physician interested in teaching and providing excellent medical care. Accredited hospital in scenic southeast Alaska. 12 years of Family Medicine students and residents through WAMI program. Fee-for-service practice. Comprehensive benefits. Negotiable salary. Stable community with wide range of activities and opportunities. Contact David Johnson, MD, or Bill Henrickson, MD, Ketchikan Medical Clinic, Inc, 3612 Tongass Ave, Ketchikan, AK 99901; phone collect (907) 225-5145.

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GENERAL INTERNIST/NEUROMUSCULAR/COPD/REHABILITATION. Immediate opening for BC/BE General Internist to join the staff of a 48-bed respiratory unit at an internationally recognized rehabilitation center affiliated with University of Southern California. Management of respiratory-neuromuscular/chest wall disorders, COPD, and tuberculosis. Some Critical Care. Busy exercise lab. Clinical faculty appointment at USC, depending on qualifications. Interested individuals should send CV to Ahmet Baydur, MD, Chest Medicine Service, Rancho Los Amigos Medical Center, 7601 E. Imperial Hwy, Downey, CA 90242. Equal Opportunity/Affirmative Action Employer.

ACADEMIC GENERAL INTERNIST. The University of Utah School of Medicine, Division of General Medicine is offering full-time positions for BC/BE Internists at the Instructor, Assistant Professor, Associate Professor levels. Rank and salary commensurate with qualifications. Opportunities include patient care, teaching of medical students and residents, administration, and clinical research. Applications must be postmarked by May 31, 1991; applications submitted after the deadline may be considered if no qualified candidates have applied by that deadline. An equal opportunity employer. Contact Dr John H. Holbrook, MD, Department of Internal Medicine, University Hospital 4B-120, Salt Lake City, UT 84132.

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(Continued on Page 646)

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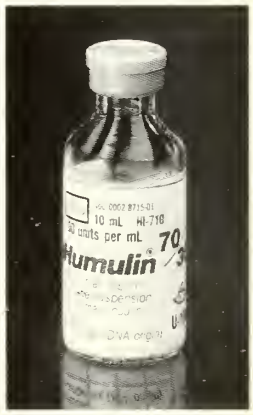

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(Continued from Page 644)

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(Continued on Page 647)

(Continued from Page 646)

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BC/BE PULMONARY/CRITICAL CARE—SAN FRANCISCO BAY AREA. Physician sought to join two busy Pulmonologists in Marin county, 10 miles north of San Francisco. Excellent opportunity to be part of a well established practice, which would include inpatient and outpatient consultation and active involvement in the Intensive and Coronary Units at a superb community hospital. Guaranteed salary and benefits are available now but we will be willing to wait for completion of training in 1991. Send CV to Alan Margolin, MD, 900 S. Eliseo Dr, Greenbrae, CA 94904.

PATHOLOGIST, BC/BE—CENTRAL CALIFORNIA VALLEY. Seven member group seeks associate for independent multiple hospital and private laboratory practice. Send CV to Robert F. Chard, MD, Delta Pathology Associates Medical Group, 2291 W. March Ln, Ste 179E, Stockton, CA 95207.

PHYSICIANS WANTED

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UNIVERSITY OF CALIFORNIA, DAVIS MEDICAL CENTER. The University of California, Davis, Department of Emergency Medicine is searching for physicians residency trained or BC in Emergency Medicine. The Health Science Campus is located in Sacramento and serves a large area of northern California. The Emergency Department cares for over 60,000 patients a year. The Center operates as a Level One Trauma Center, has paramedic base station training responsibilities, and has a helicopter service. An approved Emergency Medicine Residency Program began in July 1990. Emergency Physicians supervise medical students, interns, and residents, in addition to having direct patient responsibilities. Support for clinical research is available to those interested. University compensation is competitive, and fringe benefits include health and dental insurance, three weeks paid vacation, one week continuing medical education, social security, UC retirement plan, 12 paid holidays per year, and full malpractice coverage. Send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

TWO INTERNISTS seek an associate BE/BC Internist for busy Internal Medicine group practice located in a community of 60,000. Forty miles from San Francisco. Excellent modern hospital. Superb location in which to live and work. For more information write Thomas I. Paukert, MD, 3443 Villa Lane, Ste 6, Napa, CA 94558; (707) 252-8407.

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If you are interested in becoming part of this exciting practice, please call or send your Curriculum Vitae to: Jerry Reeves, M.D., President, Southwest Medical Associates, PO Box 15645, Las Vegas, NV 89114-5645; (702) 877-8638. Equal Opportunity Employer.

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SACRAMENTO, CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS. Opportunities available in Sacramento for BC physicians in Dermatology, Internal Medicine, Orthopedics, Ophthalmology, Otolaryngology, Psychiatry, Toxicology, and Neurology with a multispecialty medical group which provides forensic medical evaluations. This is an excellent opportunity to supplement income as well as associate with a well respected medical group whose practice is limited to evaluations. Send inquiry and CV to Terence Doyle, Disability Reporters, 2805 J St, Ste 305, Sacramento, CA 95816; (916) 444-8600.

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BC/BE FAMILY PRACTITIONER, OB-competent, for nonprofit community clinic in California redwood country. Rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

MEDICAL DIRECTOR TRAUMA SERVICES. Eden Hospital. Level II Regional Trauma Center, Alameda county. Submit CV to Trauma Services, Eden Hospital, 20103 Lake Chabot Rd, Castro Valley, CA 94546; or call Dr Peter Wong, (415) 886-0535 or Dr Brian Walker, (415) 881-8445.

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THE DIVISION OF FAMILY MEDICINE at the UCSD School of Medicine is recruiting physicians to staff clinical practices and to provide clinical supervision to residents and medical students at a variety of locations in San Diego county. Candidates should be BC in Family Medicine and licensed or eligible for licensure in the state of California. Responsibilities will include direct patient care. Salaries are competitive and commensurate with experience and qualifications. Candidates should send a CV and names of three references to David M. Baughan, MD, Director of Clinical Services, Division of Family Medicine (0807) UCSD, 9500 Gilman Dr, La Jolla, CA 92093-0807. The University of California, San Diego is an Equal Opportunity/Affirmative Action Employer.

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PHYSICIANS WANTED

NORTHERN CALIFORNIA

San Jose's leading multispecialty group is growing. We are seeking BE/BC physicians in the following specialties:

- Urgent Care
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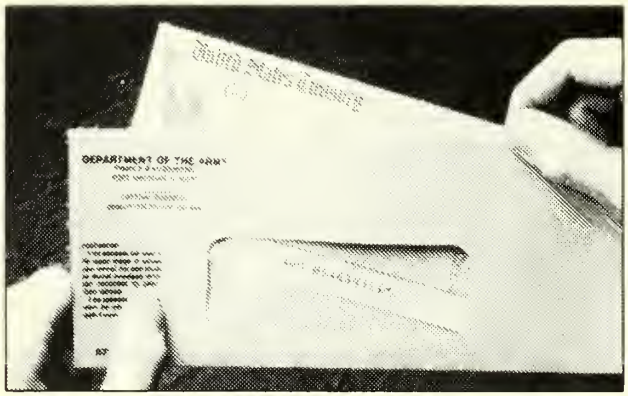

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PEDIATRIC OPPORTUNITY available on scenic central California coast close to Monterey and Santa Cruz. Private practice situation and hospital affiliation available for BC/BE Pediatrician to join with four established Pediatricians in tranquil semi-rural setting. Call-sharing arrangement and participation in modern, progressive community hospital with active maternity service and Level II Nursery. Financial incentive for first two years will cover malpractice, relocation and start-up expenses. Contact Esther Ura, Medical Staff Secretary, Watsonville Community Hospital; (408) 761-5614.

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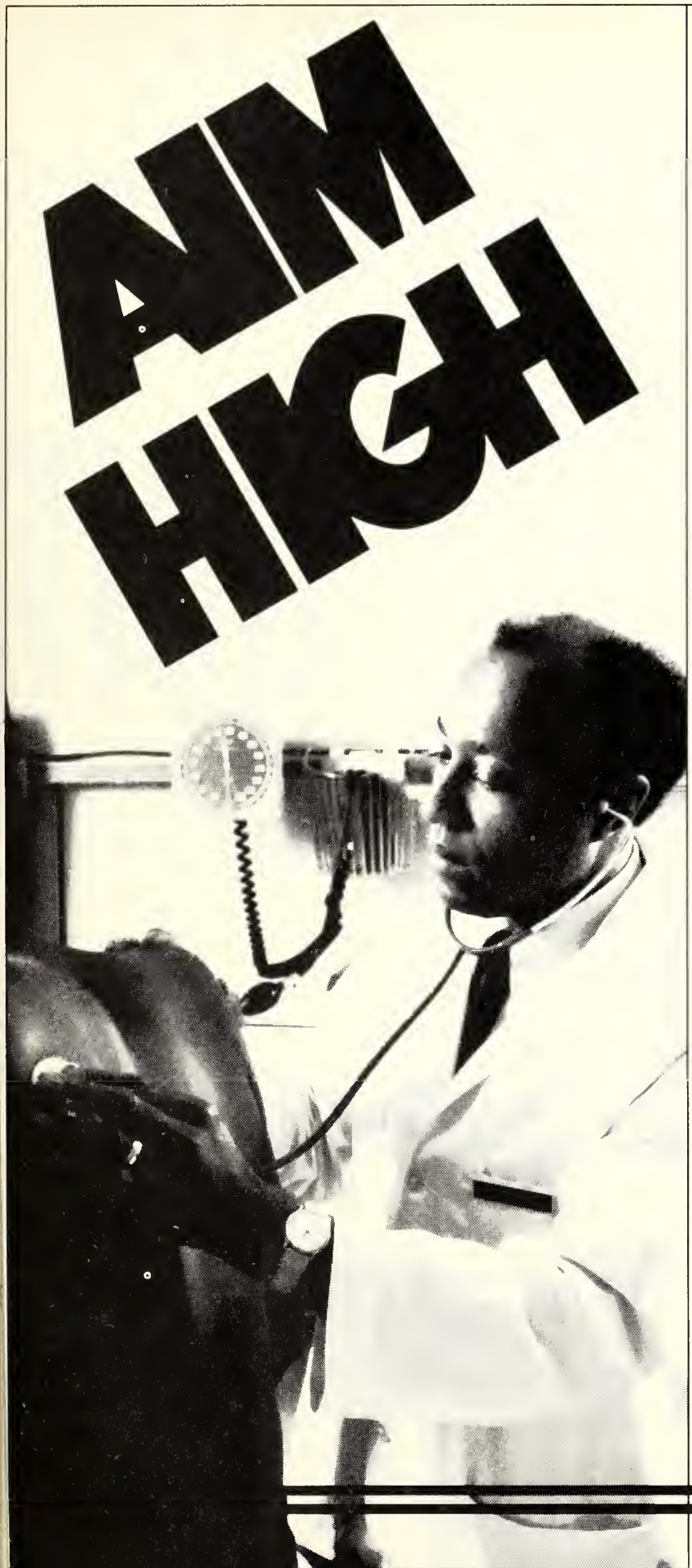

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August 1-3, 1991. San Francisco, California. Fees: $425 for ACC members; $495 for non-members; $325 for residents, fellows-in-training, nurses, and technicians. 15 Category 1 credit hours; 15 Prescribed hours AAFP. For information, call **American College of Cardiology, 1 (800) 253-4636; in Maryland, (301) 897-2695; FAX (301) 897-9745.**

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July 28-August 1, 1991. Lake Tahoe, Nevada. Fees: $475 for ACC members, $560 for non-members; $315 for residents, fellows-in-training, nurses and technicians. 21 Category 1 Credit hours. For information, call **American College of Cardiology 1 (800) 253-4636; in Maryland, (301) 897-2695; FAX (301) 897-9745.**

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August 26-28, 1991. Moran, Wyoming. Fees: $365 for ACC members; $430 for non-members; $220 for residents, fellows-in-training, nurses, technicians. 14.5 Category 1 credit hours. 14 Prescribed hours AAFP. For information, call **American College of Cardiology; 1 (800) 253-4636; in Maryland, (301) 897-2695; FAX (301) 897-9745.**

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Alaska State Medical Association—4107 Laurel St, Anchorage 99508. (907) 562-2662. Annual Meeting: 1992, date and location to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 6-8, 1991, Loews Ventana Canyon Resort, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 13-18, 1992, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 20-22, 1991, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-13, 1991, Westin Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-27, 1991, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-4, 1991, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1992, date and location to be announced.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1992, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1992, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 11-13, 1991, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, 1991, Red Lion, Bellevue.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 13-15, 1991, Jackson Lake Lodge, Moran.

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Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution)

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling)

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

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One Of A Kind

Please see Brief Summary of Prescribing Information on adjacent page.

Glaxo/ROCHE

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The Western Journal of Medicine

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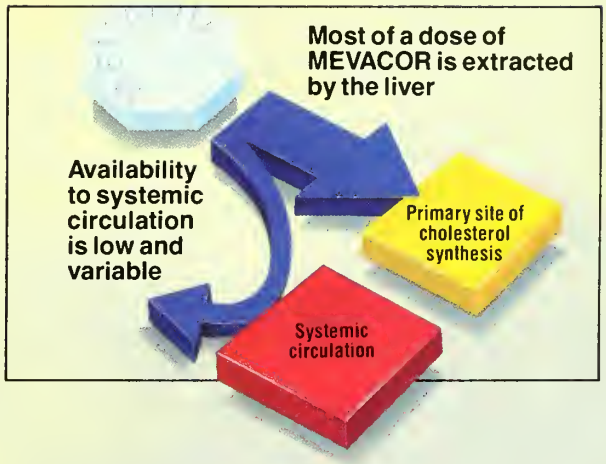
MEVACOR works where it should: at the primary site of cholesterol synthesis

HIGHLY SELECTIVE

MEVACOR is the first agent to selectively inhibit cholesterol production at the primary site of synthesis. This selective activity means MEVACOR is highly effective–with only a low and variable amount of active drug available for systemic circulation.



MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

In clinical studies, marked persistent increases (to more than three times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year. It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy, and periodically thereafter in all patients.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and slit-lamp monitoring, please refer to the Prescribing Information.

For a Brief Summary of Prescribing Information, please see the back of this advertisement.

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For many patients with primary hypercholesterolemia (Types IIa and IIb), when diet and other nondrug therapies are inadequate

MEVACOR®
(LOVASTATIN | MSD)

TABLETS, 20 mg 40 mg

MSD
MERCK SHARP & DOHME

MEVACOR®
(LOVASTATIN | MSD)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication

Active liver disease or unexplained persistent elevations of serum transaminases

Pregnancy and lactation

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction*: **Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS).** When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Several cases of rhabdomyolysis have been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness, or weakness, and or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy, the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General*. Before instituting therapy with MEVACOR® (Lovastatin, MSD), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Eye: There was a high prevalence of baseline lenticular opacities in the patient population included in the clinical trials with lovastatin. During these trials the appearance of new opacities was noted. The causal relationship of lovastatin to these findings has not been established.

Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase. There was no clinically significant change in visual acuity in the patients who had new opacities reported, nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity. Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastatin therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin*. See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

A statistically significant increase ($p \leq 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose), no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (62.5 and 312 times the maximum recommended human dose), no increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region, acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat; however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadjusted $p = 0.025$). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose – about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers: Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin, MSD) is generally well tolerated. Adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR, about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences: Adverse experiences reported in patients treated with MEVACOR in controlled clinical studies are shown in the table below:

	MEVACOR (N = 613) %	Placebo (N = 82) %	Cholestyramine (N = 88) %	Probucol (N = 97) %
Gastrointestinal				
Constipation	4.9	—	34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9	—	13.6	3.1
Flatus	6.4	2.4	21.6	2.1
Abdominal pain/cramps	5.7	2.4	5.7	5.2
Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1.0
Headache	9.3	4.9	4.5	8.2
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	3.1
Dysgeusia	0.8	—	1.1	—

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9% and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

Uncontrolled Clinical Studies: The adverse experiences observed in uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function tests were observed at a higher incidence than in the controlled studies (see WARNINGS, *Liver Dysfunction*). Myopathy (myalgia with marked CPK elevations) was reported in approximately 0.5% of patients (see WARNINGS, *Skeletal Muscle*).

Causal Relationship Unclear. *Nervous System*: Peripheral neuropathy has been reported, the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

Special Senses: Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase (see PRECAUTIONS).

Post-marketing Experience: Additional adverse experiences occurring since the drug was marketed are listed below:

Clinical Adverse Experiences

Gastrointestinal: Hepatitis, cholestatic jaundice, anorexia, vomiting.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, flushing, malaise, and dyspnea.

Nervous System/Psychiatric: Psychic disturbances, including anxiety, paresthesia.

Skin: Erythema multiforme, including Stevens-Johnson syndrome, toxic epidermal necrolysis.

Causal Relationship Unknown

Gastrointestinal: Pancreatitis, stomatitis.

Skin: Alopecia.

Nervous System/Psychiatric: Depression, insomnia.

Metabolic: Edema.

Clinical Laboratory Test Findings

Liver Function Tests: Liver function test abnormalities, including elevated alkaline phosphatase and bilirubin.

Thyroid Function Tests: Rare reports of thyroid function test abnormalities in patients taking concomitant thyroxine.

OVERDOSAGE: The oral LD_{50} of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* for dose response results).

For those patients with severely elevated serum cholesterol levels (i.e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at 40 mg/day.

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), the maximum recommended dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

MSD
MERCK SHARP & DOHME

For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. JOMC48R(510)

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JUN 20 1991

In Memoriam

California Medical Association

Barrows, William T., San Diego. Died Feb 9, 1991, aged 81. Graduate of College of Osteopathic Physicians and Surgeons, 1933, and University of California, Irvine, 1962. Dr Barrows was a member of the San Diego County Medical Society.

Bechtel, Edward J., Newport Beach. Died Jan 14, 1991, aged 66. Graduate of University of Southern California School of Medicine, Los Angeles, 1952. Licensed in California in 1952. Dr. Bechtel was a member of the Orange County Medical Association.

Burke, Robert H., Oakland. Died Mar 27, 1991, aged 66. Graduate of State University of New York at Buffalo, 1951. Licensed in California in 1952. Dr Burke was a member of the Alameda-Contra Costa Medical Association.

Cameron, Stuart A., Patton. Died Dec 27, 1990, aged 89. Graduate of University of Illinois College of Medicine, Chicago, 1926. Licensed in California in 1926. Dr Cameron was a member of the San Bernardino County Medical Society.

Carnay, Laurence, Paramount. Died Jan 16, 1991, aged 49. Graduate of Cornell University Medical College, New York, 1966. Licensed in California in 1972. Dr Carnay was a member of the Los Angeles County Medical Association.

Drucker, Arnold P., San Mateo. Died Mar 1, 1991, aged 74. Graduate of University of Illinois College of Medicine, Chicago, 1941. Dr Drucker was a member of the San Mateo County Medical Society.

Fisichella, Dominick, San Francisco. Died Feb 16, 1991, aged 42. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1974. Dr Fisichella was a member of the San Francisco Medical Society.

Gibbons, Henry, San Francisco. Died Feb 10, 1991, aged 84. Graduate of Stanford University, 1931. Licensed in California in 1931. Dr Gibbons was a member of the San Francisco Medical Society.

Green, Chester F., Oakland. Died Mar 19, 1991, aged 86. Graduate of University of Nebraska, Omaha, 1936. Dr Green was a member of the Alameda-Contra Costa Medical Association.

Greenlea, Lloyd S., La Canada. Died Jan 30, 1991, aged 80. Graduate of Loma Linda University, Loma Linda, California, 1935. Licensed in California in 1935. Dr Greenlea was a member of the Los Angeles County Medical Association.

Hine, Charles Henry, San Francisco. Died Feb 26, 1991, aged 73. Graduate of University of Wisconsin Medical School, Madison, 1943. Licensed in California in 1946. Dr Hine was a member of the San Francisco Medical Society.

Huwe, Eugene L., Anaheim. Died Feb 1, 1991, aged 81. Graduate of University of Cincinnati. Dr Huwe was a member of the Orange County Medical Association.

Kodras, Donald Alan, San Diego. Died Jan 1, 1991, aged 38. Graduate of University of Kansas School of Medicine, Kansas City, 1978. Dr Kodras was a member of the San Diego County Medical Society.

Lansing, Carl V., Crescent City. Died Mar 14, 1991, aged 80. Graduate of Loma Linda University, 1944. Dr Lansing was a member of the Humboldt-Del Norte Medical Society.

Morgan, Louis Starner, San Jose. Died Feb 23, 1991, aged 40. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1974. Licensed in California in 1979. Dr Morgan was a member of the Santa Clara County Medical Association.

Nickels, Thomas T., Oakland. Died Feb 13, 1991, aged 78. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1938. Dr Nickels was a member of the Alameda-Contra Costa Medical Association.

Reed, Elizabeth B., San Francisco. Died Feb 12, 1991, aged 67. Graduate of University of California, 1953. Licensed in California in 1954. Dr Reed was a member of the San Francisco Medical Society.

Richardson, Hildreth L., Los Gatos. Died Mar 6, 1991, aged 71. Graduate of University of California, Irvine, California College of Medicine, 1960. Dr Richardson was a member of the Santa Clara County Medical Association.

Struver, Gerd P., San Francisco. Died Jan 11, 1991, aged 61. Graduate of University of Chicago-Pritzker School of Medicine, 1959. Licensed in California in 1960. Dr Struver was a member of the San Francisco Medical Society.

Vetromile, Gerard A., Pleasant Hill. Died Mar 10, 1991, aged 80. Graduate of Boston University, 1935. Licensed in California in 1964. Dr Vetromile was a member of the Orange County Medical Association.

Weinstein, M. Lawrence, Anaheim. Died Feb 4, 1991, aged 68. Graduate of Loyola University, Maywood, Illinois, 1950. Dr Weinstein was a member of the Orange County Medical Association.

Wilder, E. Anne, San Francisco. Died Feb 5, 1991, aged 70. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1958. Licensed in California in 1950. Dr Wilder was a member of the San Francisco Medical Society.

Denver Medical Society

Bremers, Harold Henry. Died Mar 15, 1991, aged 69. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1948. Licensed in Colorado in 1949.

Buck, George R. Died Feb 24, 1991, aged 86. Graduate of University of Colorado School of Medicine, Denver, 1931. Licensed in Colorado in 1931.

Fralick, E. Howard. Died Mar 7, 1991, aged 76. Graduate of University of Colorado School of Medicine, Denver, 1940. Licensed in Colorado in 1940.

Harvey, Robert Philip. Died Feb 11, 1991, aged 81. Graduate of University of Colorado School of Medicine, Denver, 1936. Licensed in Colorado in 1936.

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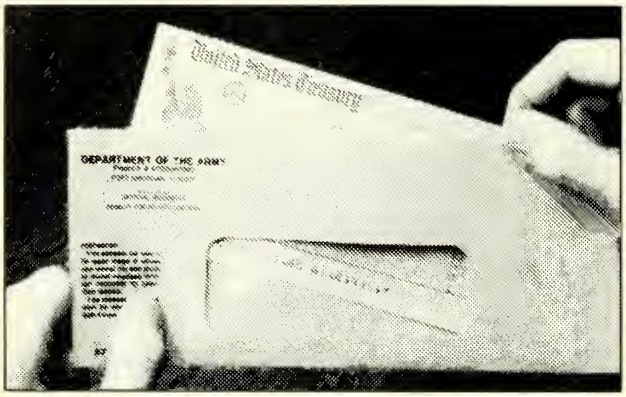

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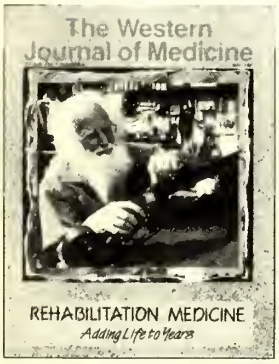

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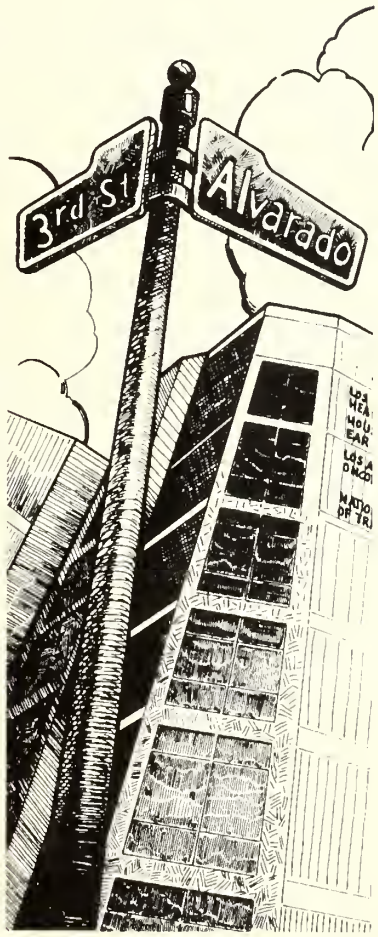

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
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3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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References: 1. Newton RE, *et al*: A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21. 2. Luckhi, *et al*: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. 3. Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance:*** Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

***Information for Patients*—**Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding, and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations; nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only if clearly needed.

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials*—**Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

***Other Events Observed During the Entire Premarketing Evaluation*—**The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia; increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

***Postintroduction Clinical Experience*—**Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

***Physical and Psychological Dependence*—**Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

***Recommended Overdose Treatment*—**General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

MJL8-4270

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IN LOWER RESPIRATORY INFECTIONS

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amoxicillin/clavulanate potassium

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*Please see brief summary of prescribing information on adjacent page. Clinical success rate for bronchitis and pneumonia was 98%. Data on file, Medical Department, SmithKline Beecham Pharmaceuticals.

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Brief Summary of Prescribing Information

AUGMENTIN amoxicillin/clavulanate potassium

Indications and Usage *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below

Lower Respiratory Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp and *Enterobacter* spp

While *Augmentin* is indicated only for the conditions listed above infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above Once the results are known therapy should be adjusted, if appropriate

Contraindications A history of allergic reactions to any penicillin is a contraindication

WARNINGS SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS IF AN ALLERGIC REACTION OCCURS *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED**

Precautions General While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics periodic assessment of organ system functions, including renal hepatic and hematopoietic function, is advisable during prolonged therapy

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy If superinfections occur (usually involving *Pseudomonas* or *Candida*) the drug should be discontinued and/or appropriate therapy instituted

Drug Interactions Probenecid decreases the renal tubular secretion of amoxicillin Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients There are no data with *Augmentin* and allopurinol administered concurrently *Augmentin* should not be co-administered with Antabuse® (disulfiram)

Carcinogenesis, Mutagenesis, Impairment of Fertility Long term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential

Pregnancy (Category B) Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin* There are however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Labor and Delivery Oral ampicillin class antibiotics are generally poorly absorbed during labor Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary

Nursing Mothers Ampicillin class antibiotics are excreted in the milk therefore, caution should be exercised when *Augmentin* is administered to a nursing woman

Adverse Reactions *Augmentin* is generally well tolerated The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug related side effects The most frequently reported adverse effects were diarrhea/loose stools (9%) nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%)

The overall incidence of side effects and in particular diarrhea, increased with the higher recommended dose Other less frequently reported reactions include abdominal discomfort, flatulence and headache

The following adverse reactions have been reported for ampicillin class antibiotics

Gastrointestinal Diarrhea, nausea vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue enterocolitis and pseudomembranous colitis

Hypersensitivity reactions Skin rashes, urticaria angioedema serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia myalgia, and frequently fever) erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported These reactions may be controlled with antihistamines and if necessary, systemic corticosteroids Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings)

Liver A moderate rise in SGOT SGPT, AST, and/or ALT has been noted in patients treated with ampicillin class antibiotics including *Augmentin* The significance of these findings is unknown As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely with the predominant effects being cholestatic hepatocellular, or mixed cholestatic-hepatocellular Signs/symptoms may appear during or after therapy and they resolve completely over time

Hemic and Lymphatic Systems Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia leukopenia and agranulocytosis have been reported during therapy with penicillins These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*

Central Nervous System Reversible hyperactivity, agitation, anxiety, insomnia, confusion behavioral changes, and/or dizziness have been reported rarely

Dosage Adults The usual adult dose is one *Augmentin* '250' tablet every eight hours For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* '500' tablet every eight hours

Since both the *Augmentin* '250' and '500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* '250' tablets are not equivalent to one *Augmentin* '500' tablet Therefore, two *Augmentin* '250' tablets should not be substituted for one *Augmentin* '500' tablet for treatment of more severe infections

Children The usual dose is 20 mg/kg/day based on amoxicillin component, in divided doses every eight hours For otitis media, sinusitis and other more severe infections the dose should be 40 mg/kg/day based on the amoxicillin component in divided doses every eight hours Also available as *Augmentin* '125' and '250' chewable tablets

Children weighing 40 kg and more should be dosed according to the adult recommendations

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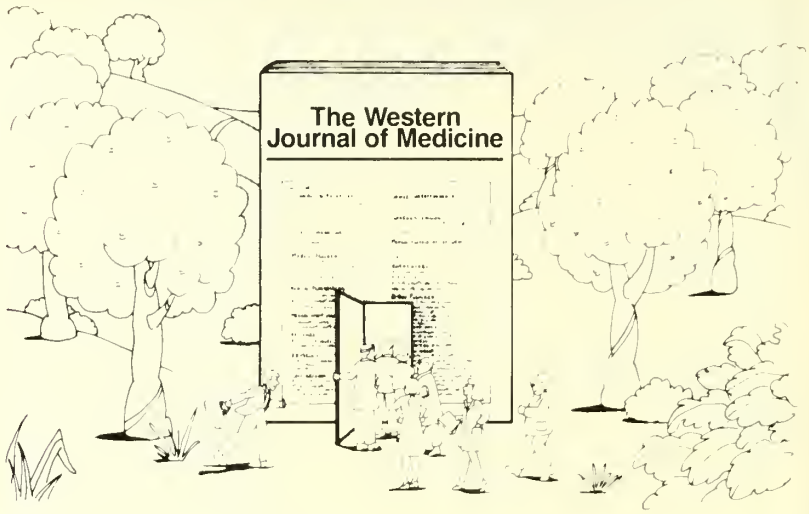
Inside Information



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1-YEAR INDICATION FOR DAILY THERAPY

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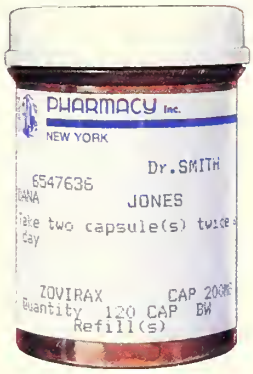

*Alternate maintenance regimens range from 200 mg t.i.d. to 200 mg five times daily.

†In a controlled study of 3 years' duration, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively.[3]

Please see brief summary of prescribing information on adjacent page.

ZOVIRAX®
(acyclovir) capsules

KEEPS HERPES PATIENTS LESION-FREE LONGER†

ZOVIRAX® CAPSULES
ZOVIRAX® SUSPENSION
(ACYCLOVIR)

BRIEF SUMMARY

INDICATIONS AND USAGE: Zovirax Capsules and Suspension are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients

Zovirax Capsules and Suspension are also indicated for the acute treatment of herpes zoster (shingles)

Genital Herpes Infections: The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy The physical, emotional and psycho-social difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs Thus orally administered Zovirax is not appropriate in treating all genital herpes infections The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes)

Double-blind, placebo-controlled studies have demonstrated that orally administered Zovirax significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing The duration of pain and new lesion formation was decreased in some patient groups The promptness of initiation of therapy and/or the patient's prior exposure to Herpes simplex virus may influence the degree of benefit from therapy Patients with mild disease may derive less benefit than those with more severe episodes In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous Zovirax

Recurrent Episodes

Double-blind, placebo-controlled studies in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered Zovirax given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients

In a study of 283 patients who received 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52% and 63% of patients remained free of recurrences in the first, second and third years, respectively Serial analyses of the 3 month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time

The frequency and severity of episodes of untreated genital herpes may change over time After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of acyclovir therapy Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects In general, orally administered Zovirax should not be used for the suppression of recurrent disease in mildly affected patients Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see Carcinogenesis, Mutagenesis, Impairment of Fertility) should be borne in mind when designing long-term management for individual patients Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease Thus, this regimen should be considered only for appropriate patients with annual re-evaluation

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions

Herpes Zoster Infections: In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to Zovirax and 94 to placebo), Zovirax (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to Zovirax and 43 to placebo), Zovirax (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia or hyperesthesia)

CONTRAINDICATIONS: Zovirax Capsules and Suspension are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations

WARNINGS: Zovirax Capsules and Suspension are intended for oral ingestion only

PRECAUTIONS General: Zovirax has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see PRECAUTIONS — Carcinogenesis, Mutagenesis, Impairment of Fertility) The recommended dosage should not be exceeded (see DOSAGE AND ADMINISTRATION)

Exposure of Herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses The possibility of the appearance of less sensitive viruses in man must be borne in mind when treating patients The relationship between the *in vitro* sensitivity of Herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see CLINICAL PHARMACOLOGY Microbiology)

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve Urinary excretion and renal clearance were correspondingly reduced The clinical effects of this combination have not been studied

Carcinogenesis, Mutagenesis, Impairment of Fertility The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes) Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics)

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors At 450 mg/kg/day plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay

Acyclovir was tested in two *in vitro* cell transformation assays Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters, higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels) In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels) In all 4 microbial assays, no evidence of mutagenicity was observed Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in man At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels Results in the other five mammalian cell loci follow at 3 loci in a Chinese hamster ovary cell line the results were inconclusive at concentrations at least 1850 times human levels, at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p o) or in rats (25 mg/kg/day s c) In the mouse study plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels At a higher dose in the rat (50 mg/kg/day, s c), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels) No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels) In a rat peri- and postnatal study at 50 mg/kg/day s c (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12 5 mg/kg/day and 25 mg/kg/day s c The intravenous administration of 100 mg/kg/day a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured) However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively caused testicular atrophy Plasma levels were not measured in the one month study and were 24 to 48 times human levels in the six month study Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day, some evidence of recovery of sperm production was evident 30 days postdose Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels No testicular abnormalities were seen in dogs given 50 mg/kg/day i v for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels)

Pregnancy ***Teratogenic Effects***: Pregnancy Category C Acyclovir was not teratogenic in the mouse (450 mg/kg/day p o), rabbit (50 mg/kg/day s c and i v) or in standard tests in the rat (50 mg/kg/day, s c) These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity In this test rats were given 3 s c doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels There are no adequate and well-controlled studies in pregnant women Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of Zovirax and ranged from 0 6 to 4 1 times corresponding plasma levels These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0 3 mg/kg/day Caution should be exercised when Zovirax is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Herpes Simplex: ***Short-Term Administration***: The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with orally administered Zovirax were nausea and/or vomiting in 8 of 298 patient treatments (2 7%) and headache in 2 of 298 (0 6%)

Nausea and/or vomiting occurred in 2 of 287 (0 7%) patients who received placebo

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments with orally administered Zovirax (0 3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash leg pain, inguinal adenopathy medication taste and sore throat

Long-Term Administration The most frequent adverse reactions reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 Zovirax - treated patients were nausea (4 8%), diarrhea (2 4%), headache (1 9%) and rash (1 7%) The 589 control patients receiving intermittent treatment of recurrences with Zovirax for 1 year reported diarrhea (2 7%), nausea (2 4%), headache (2 2%) and rash (1 5%)

The most frequent adverse reactions reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1 5%), rash (1 3%) and paresthesia (0 8%) Reactions reported by 329 patients during the third year include asthenia (1 2%), paresthesia (1 2%) and headache (0 9%)

Herpes Zoster The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg oral Zovirax 5 times daily for 7 to 10 days in 323 patients were malaise (11 5%) nausea (8 0%), headache (5 9%), vomiting (2 5%), diarrhea (1 5%) and constipation (0 9%) The 323 placebo recipients reported malaise (11 1%), nausea (11 5%), headache (11 1%), vomiting (2 5%), diarrhea (0 3%) and constipation (2 4%)

OVERDOSAGE Precipitation of acyclovir in renal tubules may occur when the solubility (2 5 mg/mL) in the intratubular fluid is exceeded Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species rats treated with i v and i p doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s c doses of 100 mg/kg/day for 10 days, rabbits at s c and i v doses of 50 mg/kg/day for 13 days, and dogs at i v doses of 100 mg/kg/day for 31 days A 6 hr hemodialysis results in a 60% decrease in plasma acyclovir concentration Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood In the event of acute renal failure and anuria the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION)

DOSAGE AND ADMINISTRATION Treatment of initial genital herpes: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 10 days

Chronic suppressive therapy for recurrent disease: 400 mg (two 200 mg capsules or two teaspoonfuls [10 mL] suspension) 2 times daily for up to 12 months, followed by re-evaluation See INDICATIONS AND USAGE and PRECAUTIONS for considerations on continuation of suppressive therapy beyond 12 months Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily

Intermittent Therapy: 200 mg (one 200 mg capsule or one teaspoonful [5 mL] suspension) every 4 hours, 5 times daily for 5 days Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules or four teaspoonfuls [20 mL] suspension) every 4 hours orally 5 times daily for 7 to 10 days

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications

Normal Dosage Regimen (5x daily)	Creatinine Clearance (mL/min/1 73m²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval (hrs)
200 mg every 4 hours	> 10	200	every 4 hours 5x daily
	0-10	200	every 12 hours
800 mg every 4 hours	> 25	800	every 4 hours 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

For patients who require hemodialysis, the dosing schedule should be adjusted so that a dose is administered after each dialysis

References: 1. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection: a multicenter double-blind trial. *JAMA*. 1988;260:201-206. **2.** Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med*. 1988;85(suppl 2A):14-19. **3.** Data on file, Burroughs Wellcome Co., 1990.

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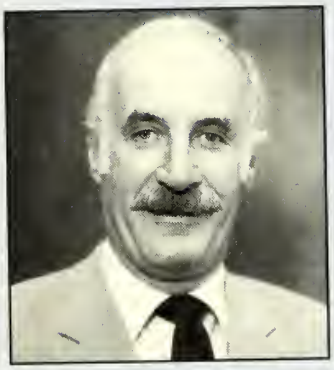

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SCHEDULE

THURSDAY, JULY 25, 1991
8:30 AM - 5:00 PM HOUSE OF DELEGATES

SCIENTIFIC SESSION—FRIDAY, JULY 26, 1991

7:45 AM WELCOME—*David M. Barton, MD*

8:00 AM RHEUMATOID ARTHRITIS
James Louie, MD
Chief, Division of Rheumatology,
UCLA School of Medicine

8:50 AM GASTROESOPHAGEAL REFLUX DISORDERS
Michael Levitt, MD
Associate Chief of Staff for Research
VAMC Minneapolis, Professor of Medicine,
University of Minnesota

9:40 AM RECESS TO REVIEW EXHIBITS

10:10 AM CA RISK FACTORS IN ESTROGEN REPLACEMENT
R. Donald Gambrell, Jr., MD
Clinical Professor, Department of Endocrinology,
Medical College of Georgia

11:00 AM PHYSICIAN CONCERNS: ETHICS OF AIDS
Roy Schwarz, MD
Senior Vice President, Medical Education and Science,
American Medical Association

11:50 AM MORNING WRAP-UP

12:00 NOON LUNCH BREAK

1:30 PM GAS AND BLOATING
Michael Levitt, MD

2:20 PM RENOIR: HIS ART AND HIS ARTHRITIS
James Louie, MD

3:00 PM OSTEOARTHRITIS AND ESTROGEN
R. Donald Gambrell, Jr., MD

SATURDAY, JULY 27, 1991
8:30 AM CLOSING SESSION, HOUSE OF DELEGATES

Registration Fee: $150.00 for non-IMA members and out-of-state physicians
For Information Contact: Idaho Medical Association, P.O. Box 2668, Boise, ID 83701
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Chief
Division of Rheumatology
UCLA School of Medicine

Michael Levitt, MD
Associate Chief of
Staff for Research
VAMC Minneapolis
Professor of Medicine
University of Minnesota

R. Donald Gambrell, Jr., MD
Clinical Professor
Department of Endocrinology
Medical College of Georgia

Roy Schwarz, MD
Senior Vice President
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Idaho Medical Association
July 25-27, 1991
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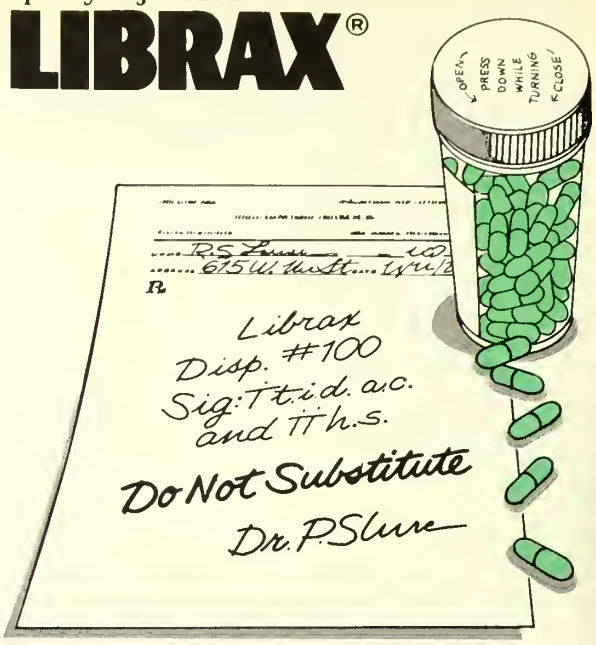

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
***Usage in Pregnancy*: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Revised: February 1988

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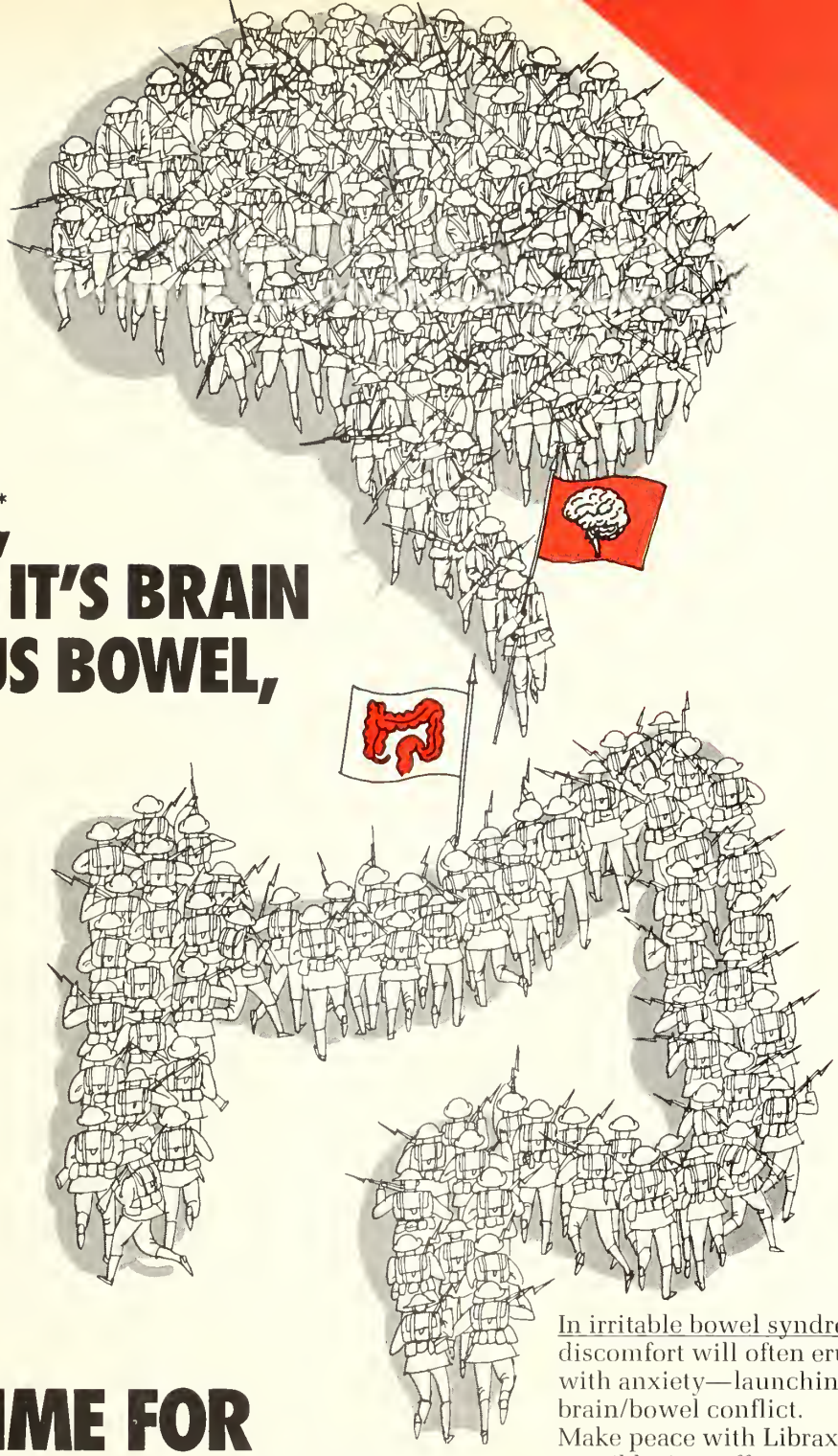

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ANESTHESIOLOGY

September 7-8—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Horizon Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, Ste 410, Foster City. (800) 345-3691.

November 3-9—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Hotel, Poipu Beach, Kauai, Hawaii. 1 week. 20 hrs. $415. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

November 8-10—**Anesthesiology Update: 1991.** UCD at Monterey Plaza Hotel, Monterey. Fri-Sun. 14 hrs. $370. Contact: UCD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

CARDIOLOGY

June 21-22—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 1-3—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

August 2-4—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Hotel, Monterey. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 16-18—**Cardiac Diagnostic Methods and Risk Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

October 10-12—**Cardiology Update: 1991.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. 12.5 hrs. $440. Contact: ACC, Extramural Programs, Dept 5080, Washington, DC 20061-5080. (800) 253-4636.

October 17-19—**Tenth Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $395. Contact: UCSF.

October 18-19—**Coronary Heart Disease Update.** Medical Education Resources at Parc Fifty Hotel, San Francisco. Fri-Sat. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

October 18-19—**Cardiology for the Clinician.** Memorial/UCI Center for Health Education. Fri-Sat. Contact: UCI.

November 8-9—**Coronary Interventions: 1991.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Fri-Sat. 14 hrs. $550. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

DERMATOLOGY

July 11-14—**Advanced Seminars in Dermatology.** UCSF at Quail Valley Lodge, Carmel. Thurs-Sun. Contact: UCSF.

July 16-20—**Dr. Hugh Greenway's Seventh Annual Conference: Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation/UCSD at Scripps Clinic, La Jolla. Tues-Sat. 36 hrs. $1100. Contact: Susan J. Buntjer, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

July 19-21—**Contact Dermatitis: The Basics.** Stanford at Hotel Meridien, San Francisco. Fri-Sun. Contact: Pamela Bain, Dept of Dermatology, Room R-122, Stanford 94305. (415) 723-7854.

August 16-20—**Fifth Annual Hot Spots in Dermatology: Masters Under the Mango Trees.** The Hawaii Dermatology Society and the Kauai Foundation at the Kaluakoi Hotel, Kepuhi Beach, Molokai, Hawaii. Fri-Tues. Contact: David Elpern, MD, Box 457, Kalaheo, HI 96741. (808) 245-1505.

November 8-10—**Pediatric Dermatology and Wound Management: Above and Below the Surface.** Children's Hospital Oakland at Monterey Conference Center, Monterey. Fri-Sun. 12 hrs. $300. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

EMERGENCY MEDICINE

June 24-28—**Postgraduate Institute for Primary Care & Emergency Physicians Emergency Medicine Symposium III: Pediatrics, OB/GYN, Dermatology, Legal Aspects, Etc.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $260-$485. Contact: UCSD.

August 1-3—**Debates and Updates in Pediatric Emergency Medicine.** UCSF at San Francisco Hilton Hotel, San Francisco. Thurs-Sat. 16 hrs. Contact: UCSF.

August 7-11—**Wilderness Medicine: '91.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Program Director, Box 321, Yreka 96097. (800) 888-5632.

August 19-23—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott, La Jolla. Mon-Fri. 32 hrs. $485. Contact: UCSD.

August 23-26—**Advances in Emergency Medicine.** Kaiser Permanente at Grand Hyatt Wailea Resort and Spa, Maui, Hawaii. Fri-Mon. Contact: Pat Salber, MD, Kaiser Permanente Hospital, 2200 O'Farrell, San Francisco 94115-3395.

October 28-November 1—**Twentieth Annual Topics in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $510. Contact: UCSF.

(Continued on Page 682)

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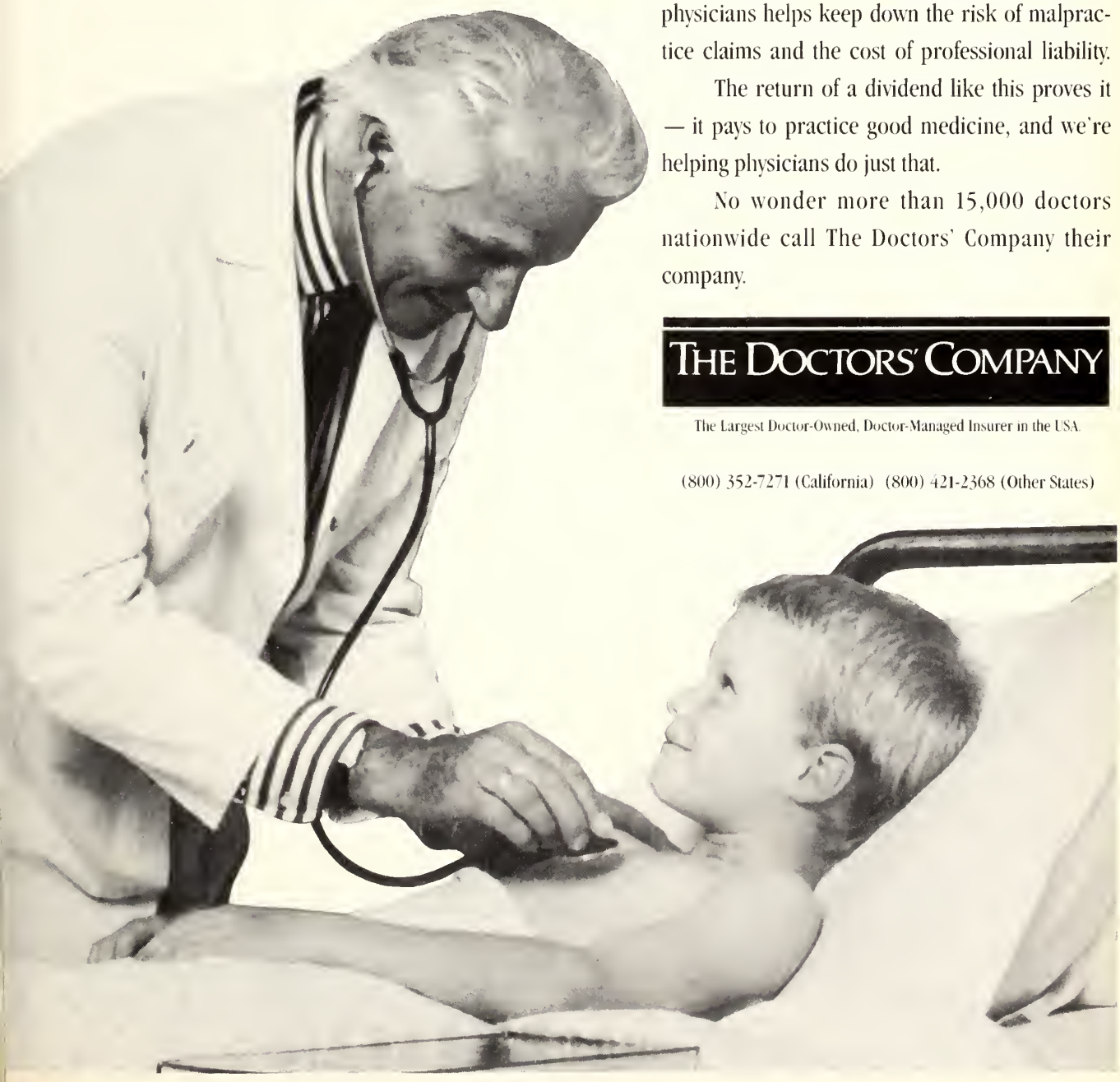

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735 Hypocholesterolemia and Malabsorption in HIV Infection
GREGG COODLEY, MD, and MARCIA KERENSKY COODLEY, MD

735 The International Medical Corps
ROBERT R. SIMON, MD

736 Preventing the Contact Dermatitis Caused by a Transdermal Clonidine Patch
JOHN A. McCHESNEY, MD

736 Possible Complications of Acupuncture
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FAMILY PRACTICE/PRIMARY CARE

July 8-11—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

August 23-25—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

October 2-4—**Sixth Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 19 hrs. $465. Contact: UCSF.

October 18-20—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

June 15—**Lyme Disease Symposium.** Kaiser Permanente Northern California at El Rancho Tropicana Convention Center, Santa Rosa. Sat. 5 hrs. Contact: Joyce Appelbaum, 1950 Franklin, Oakland 94612. (415) 987-4726.

August 1-3—**4th Annual New Advances in Common Neurologic Disorders.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. $300. Contact: Shirley Kolkey, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

August 18-23—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. $460. Contact: UCD.

August 26-28—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

August 26-30—**Internal Medicine Board Review.** Stanford University Medical Center. Mon-Fri. Contact: STAN.

September 20-22—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sun. 18 hrs. $420. Contact: UCSF.

September 28—**Pain: Diagnosis, Treatment and Management.** Scripps Clinic and Research Foundation, La Jolla. Sat. 19 hrs. $75. Contact: Laurel Steigerwald, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

October 14-20—**Seventeenth Annual Lymphoma Course.** Scripps Clinic and Research Foundation, La Jolla. Mon-Fri. 25 hrs. $550. Contact: Laurel Steigerwald, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

November 7-9—**San Francisco Otology Update: 1991.** UCSF. Thurs-Sat. 22 hrs. Contact: UCSF.

November 21-23—**3rd Annual Symposium on Diagnosis and Treatment of Bone and Soft Tissue Tumors.** UCD at Hyatt Regency, Sacramento. Thurs-Sat. Contact: UCD.

OB/GYN

July 28-31—**4th Annual In Vitro Fertilization and Embryo Transfer: A Comprehensive Update—1991.** Sun-Wed. 15 hrs. $675. Contact: UCLA Extension.

July 31—**9th Controversies in OB/GYN.** Memorial/UCI Center for Health Education in Hawaii. Wed-Sat. Contact: UCI.

August 9-11—**4th Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: Memorial/UCI Center for Health Education, Box 1428, Long Beach 90801. (213) 595-3811.

August 16-18—**Office Gynecology for the Primary Care Physician.** San Diego State University at the Hyatt Islandia, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

September 26-29—**Advanced Fetal Heart Rate Monitoring.** Memorial/UCI Center for Health Education. Thurs-Sun. Contact: UCI.

October 4-6—**3rd Annual Advanced Obstetrical & Transvaginal Ultrasound.** Memorial/UCI Center for Health Education at Doubletree Hotel/UCI Medical Center, Orange. Fri-Sun. Contact: UCI.

OCCUPATIONAL/ENVIRONMENTAL

June 15 & 22—**Workers' Compensation Seminar.** American College of Occupational Medicine in San Francisco. Sat. 6 hrs. $150. Contact: California Workers' Compensation Institute. (415) 981-2107.

October 10-13—**35th Annual Western Occupational Health Conference: Changing Themes in Occupational Medicine.** Western Occupational Medical Association at Doubletree Hotel, Monterey. Thurs-Sun. Contact: Kate Larsen, (415) 764-4803.

October 21-25—**Sports Medicine Update.** Memorial/UCI Center for Health Education in Hawaii. Mon-Fri. Contact: UCI.

October 21-November 1—**Occupational and Environmental Medicine: Session II.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

October 28-November 1—**Advances in Occupational and Environmental Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

OPHTHALMOLOGY

September 13-15—**Uveitis and Retina Frontiers—Diagnostic, Medical and Surgical Approaches.** UCSF at Carmel Valley Ranch Resort. Fri-Sun. Contact: UCSF.

October 13-17—**Joint Meeting of the American Academy of Ophthalmology and Pan-American Association of Ophthalmology** at Anaheim Convention Center. Sun-Thurs. Contact: AAO, PO Box 7424, San Francisco 94120. (415) 561-8500.

PATHOLOGY

July 15-19—**Advances in Gastroenterology.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 19-22 hrs. $425. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 9-10—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684.

October 12—**Thirty-first Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott, La Jolla. Sat. Contact: Sylvie Tarro, (213) 641-8152.

PEDIATRICS

June 21-23—**Current Concepts in Child Neurology.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 15 hrs. Contact: Children's Hospital, (619) 576-4072.

August 19-21—**Pediatrics Update: 1991.** San Diego State University at the Hyatt Islandia, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

September 13-14—**Ambulatory Pediatrics.** UCD at Radisson Hotel, Sacramento. Fri-Sat. 12 hrs. Contact: UCD.

October 16-19—**16th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Wed-Sat. Contact: UCI.

November 20-23—**Pediatric Infectious Disease Seminar.** University of Toronto at Four Seasons Hotel, Newport Beach. Wed-Sat. Contact: University of Toronto, Medical Science Bldg, Toronto, Ontario M5S 1A8. (416) 978-2718.

PSYCHIATRY

July 27-28—**Treatment of Sexual Problems of Adults Molested as Children.** UCLA at Beverly Hilton Hotel. Sat-Sun. 13 hrs. $275. Contact: UCLA.

November 8-10—**37th Annual Group Therapy Symposium.** UCSF at Handlery Union Square Hotel, San Francisco. Fri-Sun. Contact: UCSF.

RADIOLOGY

July 18-21—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, Coronado. Thurs-Sun. 19.5 hrs. $400. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-24—**Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Wed. 14 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-27—**5th Annual MRI Symposium Including: Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Sat. 31 hrs. $695. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

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July 25-28—**5th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 18 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 29-August 2—**MRI: Musculoskeletal/Body.** UCSF at Hyatt Regency, Kauai, Hawaii. Mon-Fri. 22 hrs. $595. Contact: UCSF.

August 4-8—**Napa Valley Imaging Update-MRI 1991.** UCD at Silverado Country Club, Napa. Sun-Thurs. 17 hrs. $465. Contact: UCD.

August 12-16—**Radiology for Clinicians.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 11-13—**The 7th Annual Sonography Update Conference and Exhibit.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. 18 hrs. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 14-15—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 23-26—**Applied Ultrasound: Accent on Doppler.** University of Alabama at Birmingham at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 25-28—**Diagnosis of Musculoskeletal Disorders: State of the Art.** International Skeletal Society at Hotel del Coronado, San Diego. Wed-Sat. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 2-6—**Current Concepts of Magnetic Resonance Imaging/Physics.** Stanford University Medical Center at Silverado Hotel, Napa Valley. Wed-Mon. 19 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 12-13—**Ultrasound: 1991.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 11 hrs. $195. Contact: UCD.

October 17-20—**1991 Annual Scientific Meeting.** Western Neuroradiological Society at Ritz Carlton Resort, Laguna Niguel. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 20—**Magnetic Resonance Angiography.** UCSF at Hyatt Regency Hotel, San Francisco. Sun. 7 hrs. Contact: UCSF.

October 21-25—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $595. Contact: UCSF.

October 26-27—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $225. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-27—**Vascular Ultrasound: State of the Art.** UCSF at Ritz-Carlton Hotel, San Francisco. Sat-Sun. 12 hrs. $285. Contact: UCSF.

October 28-November 1—**Sixteenth Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 28.25 hrs. $550. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 1-3—**11th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 15 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 4-8—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui, Hawaii. Mon-Fri. 24 hrs. $595. Contact: UCSF.

November 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

November 14-16—**3rd Triennial Symposium on New Directions in Antiviral Chemotherapy.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 19 hrs. $200. Contact: UCSF.

SURGERY

October 10-13—**Wound Management Workshop: October.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 18 hrs. $435. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 2-9—**13th International Seminar on Operative Arthroscopy.** UCLA at Ritz-Carlton, Mauna Lani Resort, Hawaii. 1 week. 37 hrs. $995. Contact: UCLA.

GENERAL/MULTIDISCIPLINARY

June 28-30—**4th Annual Conference for the Medical Office Laboratory.** San Diego State University at Red Lion, San Diego. Fri-Sun. 18 hrs. $400. Contact: Anne Wright, (619) 594-6255.

July 5—**Issues in International Health.** UCSD and Shiraz University School of Medicine Alumni at San Diego Hilton Beach & Tennis Resort. Fri. 3 hrs. $75. Contact: H. A. Ronaghy, MD, 3023 Bunker Hill St, No. 106, San Diego 92109. (619) 275-2700.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 25-27—**Community Health Traineeship.** Children's Hospital, Denver. Tues-Thurs. Contact: Christine Sievers, (303) 861-6413.

June 28-29—**Billings Perinatal Conference.** Children's Hospital of Denver at Billings, Montana. Fri-Sat. Contact: Christine Sievers, (303) 861-6413.

July 7-12—**Internal Medicine Program.** University of Colorado School of Medicine at YMCA of The Rockies, Estes Park. Sun-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9513.

July 11—**Cultural Considerations in Perinatal Nursing.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

July 22-26—**Renal Disease for the Internist and Nephrologist.** University of Colorado School of Medicine at The Given Institute, Aspen. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9513.

July 25-27—**Preparing for Reform—Proposals, Assumptions and Implications for Financing American Health Care—11th Annual Montgomery Dorsey Symposium.** Presbyterian/St. Luke's Community Foundation at Vail. Thurs-Sat. Contact: Mary Pettigrew, (303) 322-3515.

July 29-August 2—**Dynamic Psychotherapy.** University of Colorado School of Medicine at The Given Institute, Aspen. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9513.

August 2-4—**Recent Advances in Cancer Therapy.** University of Colorado School of Medicine at The Given Institute, Aspen. Fri-Sun. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 4-8—**34th Annual Pediatric Program.** University of Colorado School of Medicine, Children's Hospital, and the Colorado Chapter of the American Academy of Pediatrics at the Given Institute, Aspen. Sun-Thurs. Contact: Bobbi Rubingh, (800) 882-9153 or (303) 270-5196.

August 5-9—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

August 8—**Basic and Advanced Fetal Heart Rate Monitoring.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

August 8-11—**Pulmonary Physiology.** University of Colorado School of Medicine at The Given Institute, Aspen. Thurs-Sun. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 15-17—**Musculoskeletal Society Annual Meeting.** In association with University of Colorado School of Medicine at Snowmass. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 17-24—**Eleventh Annual Comprehensive Fine Needle Biopsy Course.** University of California, San Francisco, at Aspen's Hotel Jerome. Sat-Sat. Contact: University of California, San Francisco, School of Medicine, Extended Programs in Medical Education, (415) 476-4251.

August 19-23—**Internal Medicine Board Review.** University of Colorado School of Medicine, Denver. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 25-31—**Primary Care Orthopedics.** University of Colorado School of Medicine at The Given Institute, Aspen. Sun-Sat. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

September 5, 12, 19, 26—**Comprehensive Perinatal Nursing Course.** University of Colorado Health Sciences Center. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

September 27-28—**Montrose Fall Clinics for Physicians.** Montrose Memorial Hospital, Montrose. Fri-Sat. Contact: Kathy Holman, (303) 240-7397.

CONTACT INFORMATION

U of Colo—Contact, University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

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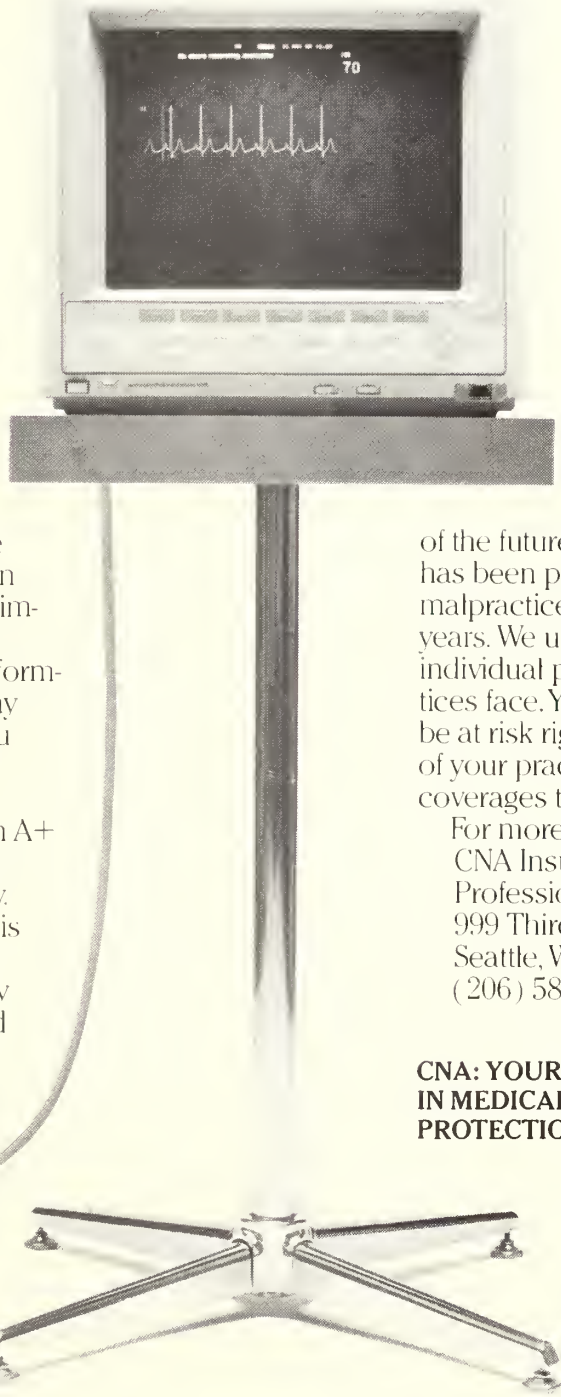

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(Continued from Page 684)

October 7-11—**Family Practice Review.** University of Colorado School of Medicine, Denver. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

October 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 7-10—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 14—**Pre-term Infant Feeding Conference.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

November 22-23—**Colorado Springs Perinatal Conference.** Children's Hospital of Denver at Colorado Springs. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

December 2-6—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

IDAHO

July 25-27—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

August 5-9—**Body Imaging: Ultrasound, CT, MR, Nuclear Medicine.** El Dorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

June 17-21—**University of Utah School on Alcoholism and Other Drug Dependencies** (Sponsor: UUSM). Mon-Fri. University of Utah, Salt Lake City. Contact: (801) 581-8664.

July 8-13—**Update in Internal Medicine: Focus on Ambulatory Care Medicine** (Sponsor: UUSM). Sat-Thurs. Snowbird. Contact: (801) 581-8664.

July 12-14—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

August 1-3—**Utah Ophthalmological Society Annual Shakespearean Festival Meeting** (Sponsor: UOS). Thurs-Sat. Southern Utah State College, Cedar City. Contact: UOS.

September 27-29—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 15—**Horizons in Urology.** Seattle. Sat. Contact: U/W.

June 18—**Treatment Needs of a High Utilizer: The Borderline Patient.** Spokane. Tues. Contact: U/W.

June 20—**Treatment Needs of a High Utilizer: The Borderline Patient.** Seattle. Thurs. Contact: U/W.

June 21—**Competency in the Confused Patient: Medical, Legal and Ethical Issues.** Seattle. Fri. Contact: VMMC.

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CONTINUING MEDICAL EDUCATION

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June 20-24—**Surviving the Elements.** Seattle. Thurs-Mon. Contact: U/W.

June 24-25—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: VMMC, (206) 627-7137.

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Articles

AIDS Awareness Among Rural Utah Physicians

BRADLEY P. NIELSEN, MD; DAVID A. GALLEGOS, MD; DONA L. HARRIS, PhD; *and* MARTA I. GOMEZ, MS, *Salt Lake City, Utah*

Studies of physicians' attitudes and knowledge of the acquired immunodeficiency syndrome (AIDS) and the clinical precautions they take against exposure to the human immunodeficiency virus (HIV) have focused on urban physicians. To determine rural physicians' knowledge and attitudes about AIDS, a questionnaire was mailed to 321 physicians practicing in rural Utah. Of the 169 physicians who completed questionnaires, 96% thought that their community or area of service had only a minor or no problem with AIDS; 89%, however, thought that their chance of seeing a patient who was HIV-positive was fair to moderate. Of the 169 respondents, 3% were not sure whether they would even treat a patient who had AIDS, 67% said they would, and 30% said they would not. Although all physicians are at risk of seeing a patient who has had exposure to HIV and other blood-borne diseases such as hepatitis B, only 55% of the respondents felt a need to take clinical precautions to prevent their exposure to the virus. Our study shows the need for all rural Utah physicians to reevaluate their risk of exposure to HIV, to increase precautionary measures for their own protection, to consider the ethical responsibility of treating AIDS patients, and to take a more active role in teaching their patients how to protect themselves from exposure to the virus.

(Nielsen BP, Gallegos DA, Harris DL, Gomez MI: AIDS awareness among rural Utah physicians. West J Med 1991 Jun; 154:689-692)

Since the outbreak of the acquired immunodeficiency syndrome (AIDS) epidemic in 1981, research has focused on identifying the virus, methods of transmission, and the means to prevent its spread in urban populations.[1,2] Little has been published concerning AIDS in rural populations in the United States, and even less is known about rural physicians' attitudes and knowledge about AIDS.

The first case of AIDS in Utah was reported in 1983. By 1985, 30 cases were known, and by 1987 the total was 91. The first rural case was reported in 1984; by 1987, there were 5 cases. Although at present the incidence of AIDS in rural areas is low, it is becoming an increasing problem.[3] To assess rural physicians' attitudes, awareness, and knowledge of AIDS and the clinical precautions they are taking to prevent exposure to the human immunodeficiency virus (HIV), we surveyed Utah physicians practicing in rural areas.

Methods

A three-page questionnaire was designed to survey all rural Utah physicians listed in the Utah state medical directory and serving populations of less than 20,000. Questions were asked about their specialties, number of years in practice, and the population of their community or area of service. They were asked about their knowledge of the signs, symptoms, transmission, and prevention of AIDS and about the types of clinical precautions they were taking in their practices. Physicians were asked what they thought their chances were of contracting HIV, whether they would treat patients who had AIDS, and whether they perceived it necessary to educate their patients about the disease. They were also asked to report whether they had made any changes in their clinical practice routines because of AIDS.

After two mailings, 186 of the 321 surveys (58%) were returned. Of these, 17 were incomplete and were excluded. The remaining 169 completed questionnaires were analyzed using the Statistical Package for the Social Sciences. Non-Gaussian distributed variables were examined using cross tabulations by exact or asymptotic Kruskal-Wallis tests.[4,5] Significance was determined at $P < .05$.

Results

Of those responding, 101 (60%) were primary care specialists with 59 (35%) family practitioners and 42 (25%) general practitioners, internists, and obstetrician-gynecologists. A surprising number of other specialists—68 (40%)—responded, including radiologists, pathologists, emergency physicians, and surgeons. More than half of the physicians (57%) had been in practice 10 years or less; an additional 25% had practiced in their communities for more than 20 years. Less than 20% had practiced between 10 and 20 years. When asked what precautions they take when doing invasive procedures, 23% indicated they only use gloves; 8% said they routinely use gloves and masks; and 33% use gloves, masks, and dispose properly of potentially contaminated material. Only 6% indicated they use goggles in addition to gloves, masks, and the proper disposal of contami-

TABLE 1.—*Correlation Between the Perception of the AIDS Problem in Physicians' Areas of Service and Their Awareness of the Need to Take Clinical Precautions**†

	AIDS Problem in Area, No. of Physicians		
Need to Take Precautions	*Moderate*	*Minor*	*No*
Yes	6	72	14
No	1	31	20
Unsure	0	15	9

AIDS = acquired immunodeficiency syndrome

*One respondent did not answer this question; therefore, the total is 168 rather than 169.
†$P = .0018$.

From the Department of Family and Preventive Medicine, University of Utah School of Medicine, Salt Lake City.
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Reprint requests to Dona L. Harris, PhD, Scholar-in-Residence, Council on Graduate Medical Education, Health Resources and Services Administration, Rockville, MD 20857.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
HIV = human immunodeficiency virus

nated material. The percentage of physicians routinely using gloves and properly disposing of contaminated material was 63%; 55% indicated they feel a need to take precautions against HIV virus in their routine contacts with their patients' blood and body fluids.

Most physicians (96%) thought that their community or area of service has a minor or no problem with AIDS. Only 4% thought that there is a moderate problem, and no physicians thought there is a severe problem. Table 1 shows the correlation between the perception of the AIDS problem in the physicians' areas of service and their awareness of the need to take clinical precautions. As they perceive an increasing problem with AIDS, more physicians feel the need to take precautions against the virus. Table 2 gives the relationship between the population of the area of service and the perceived problem with AIDS. Physicians in smaller communities were less likely to think that a problem with AIDS exists.

On a scale of 1 to 5—1 meaning none, 5 meaning high—in rating their chances of seeing a patient with the AIDS virus, most (75%) thought there was a fair chance (2 meaning fair). On the same scale, physicians rated their chance of contracting HIV in their day-to-day practice: there was a significant relationship between the size of the area of practice and their perception of the chances of contracting AIDS ($P < .04$). The physicians thought that the smaller the community, the less likely the chance of contracting the virus or of seeing a patient with AIDS.

Even after learning about AIDS, 60% of rural physicians had not changed their clinical procedures. Logistic regression analysis showed that the predictors of physicians changing their clinical procedures were physicians' knowledge of available AIDS information and services, their awareness of the need to take precautions against exposure to the virus, and their perceived chance of contracting the virus.

When questioned about an AIDS protocol in their practices, 67% indicated they had spoken with their office personnel about AIDS and 26% had established an actual protocol to be used when dealing with AIDS patients. Of the physicians with such a protocol for patients with AIDS, 68% said their protocol for AIDS patients differed from that for other patients. When asked if they would even treat patients who had AIDS, 3% were unsure, 67% said they would, and 30% would not.

The median number of AIDS tests administered per rural practice was 2. The range was from 0 (34%) to 60 (1%); the 60 tests were requested at a military depot. Of the 169 respondents, 16% indicated they had ordered between 10 and 20 tests.

When asked about their feelings toward educating their general patient population about AIDS, only 25% strongly agreed that they should, whereas 40% strongly agreed that they should educate their teenage patient population concerning the risk of contracting AIDS by sexual contact.

Respondents obtained most of their background information concerning AIDS from medical journals (91%) and continuing medical education materials (57%).

TABLE 2.—*Relationship Between the Population of the Area of Service and the Perception of the AIDS Problem**†

	AIDS Problem in Area, No. of Physicians		
Population	*Moderate*	*Minor*	*No*
0 to 10,000	1	21	24
10,000 to 15,000	0	18	6
>15,000	6	80	12

AIDS = acquired immunodeficiency syndrome

*One respondent did not answer this question; therefore, the total is 168 rather than 169.
†$P = .0001$.

Discussion

Our study shows that many rural Utah physicians feel there is not a major problem with AIDS in the populations they serve. Some physicians (31%) do not think it necessary to take routine precautions against exposure to HIV, but a few (14%) are still not sure about the need for taking even routine precautions. Thus, a substantial number of rural Utah physicians take no precautions while doing invasive procedures that could expose them to HIV and to other similarly transmitted diseases. We are concerned about such complacent behaviors by Utah's rural practitioners, many of whom are ignoring the Centers for Disease Control's (CDC) recommendations for avoiding exposure to the AIDS virus. All rural physicians should be following these recommended precautions, especially when participating in invasive procedures. Such precautions include wearing gloves, surgical masks, and protective eyewear or face shields when there is a chance of blood splashing or of droplets being generated.[6]

Health care workers in the United States have a minimal chance of being infected by HIV.[7,8] This may be one reason why physicians think they do not need to take precautions. Admittedly, there are still few cases of AIDS in rural Utah; up until 1987, only five cases had been reported. In that same time period, however, there was a substantial increase in the number of identified AIDS cases in urban Utah (Figure 1). It is likely that rural Utah will also experience such an increase as patients migrate from urban centers back to their rural homes.

Rural Utah's first case of AIDS was reported in 1984. No new cases were reported in 1985 or 1986, but in 1987 four new rural cases were reported. This may be an indication of what to expect in rural Utah during the next decade. About 118,000 Americans have already been diagnosed with AIDS (CDC cumulative annual totals),[9-15] and it has been projected that by the end of 1991, there will be 270,000 cases.[16,17] Even more alarmingly, the Public Health Service estimates that as many as 1.4 million Americans have been infected with the AIDS virus.[18] Although our study did not focus on hepatitis B, the hepatitis B virus, too, is a blood-borne organism that affects hundreds of health workers each year; therefore, physicians must recognize the importance of protecting themselves against exposure to these diseases.

Rural Utah physicians must become better educated about how HIV is spread and how physicians can protect themselves and their office personnel. The most effective educational methods identified by this study are continuing medical education and the medical literature. Our study results also suggest that the most positive predictors for physicians' changing their clinical protocols are the knowledge of available AIDS information and services, an awareness of

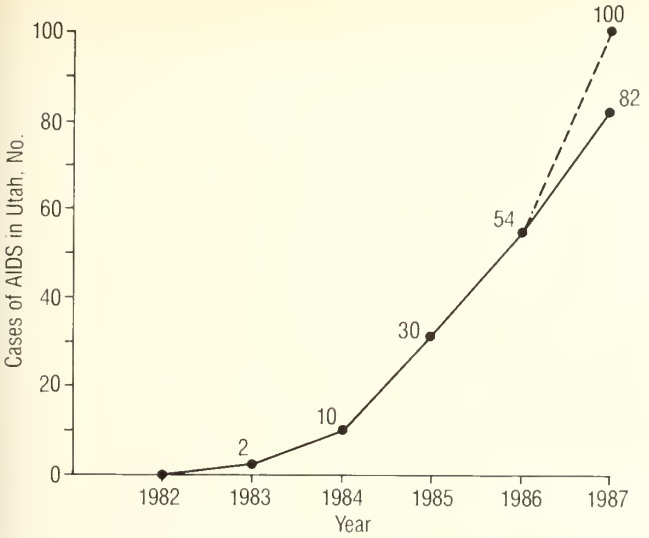

Figure 1.—The graph shows the total number of acquired immunodeficiency syndrome (AIDS) cases in Utah. The solid line indicates the number of AIDS cases according to the old Centers for Disease Control (CDC) diagnostic criteria for AIDS; the dashed line indicates the number of AIDS cases according to the new CDC diagnostic criteria.

the need to take precautions against exposure, and the perception of the chances of contracting HIV.

Almost a third (30%) of the rural physicians surveyed in this study said they would not treat a patient who had AIDS. This refusal is most likely based on many physicians' lack of experience and knowledge in the treatment of AIDS and, more important, on their fear of contracting HIV. In a 1988 survey of medical and nursing students at a large teaching hospital in the Northwest, exaggerated risk estimates were associated with a lack of knowledge and with greater resistance to working with AIDS patients.[19] It is worrisome that there is a lack of knowledge in the face of a devastating disease that needs accurate information for both patients and physicians. In 1986 the American College of Physicians and the Infectious Diseases Society of America admonished the medical schools and graduate and postgraduate programs to educate present and future physicians to care for patients who have HIV infection with compassion and a thorough knowledge base.[20] The rural physicians are an important educational link as they become office-based mentors and preceptors for current medical students. Equally troubling is the question of whether physicians are ethically bound to treat patients infected with HIV. Should the personal risk assumed in treating such patients be an acceptable reason for denying them adequate treatment? It should not. Sanford Sharp, MD, reminds physicians of their responsibility and obligation to care for these contagious patients: physicians must uphold the ethical tradition and "the moral requirements of the physician-patient relationship."[21,22] Pellegrino professes that "to refuse to care for AIDS patients, even if the danger were much greater than it is, is to abnegate what is essential to being a physician."[23]

The ethical dilemma can be compounded in particular populations. In Utah, 80% of the state's rural population is of the Mormon religion. Often a local physician is also an elder of the church. This position can easily compromise the values and ethical responsibility of the physician because the church doctrine does not allow homosexuals or bisexuals to be members of the church. When such information is available to church leaders, it can mean excommunication for the church member. Unfortunately, the first cases of AIDS were among homosexual men; therefore, the misperception remains that AIDS is a "gay disease."[20] In the study of Ficarroto and co-workers, medical and nursing students also had antihomosexual attitudes that contributed to their resistance to working with AIDS patients.[19]

The services of all physicians will be needed if the projected increases in the number of AIDS patients continue. Not only do physicians need to be educated, the general population also needs to be better informed on the ways in which the virus is transmitted. Less than half (40%) of rural Utah physicians strongly feel that teenagers should be educated about the prevention of AIDS. This is disturbing because the birth rate for white teenagers in Utah is 19% higher than the national average.[24(p1)] Because the virus is transmitted by unprotected sexual intercourse, all Utah physicians must assume a more active role in educating this sexually active population as well as other populations at high risk, such as intravenous drug users and homosexual men. Physicians have an obligation to make their knowledge available to all who need it.[23] Effective health education is the single most important approach to controlling the epidemic spread of this disease.[20]

All physicians are at risk for exposure to HIV. Clinical precautions should be taken to prevent such exposure. These study results support the need for Utah's rural physicians—indeed, rural physicians everywhere—to consider even more seriously their risk of exposure, to increase the precautionary measures taken for their own protection, and to educate their patients to prevent the spread of HIV.

A possible limitation of this study is that although less than two thirds of the population responded, generalizations are made on a return of 58%. It was felt that this was an adequate response rate, especially considering the ethical and moral sensitivity of the issue.

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THE SHULAMITE GIRL

Return, return, O Shulamite, return
that we may look upon thee.
—Solomon's Song

The doctor with Lake Tahoe in his eyes
has charts of an outlined, white-space man
whose colored meridians strike
his insides like the arrows of St. Sebastian.
The large, cement-gray-suited woman
who has driven with her son
from Sacramento sits before the doctor
and says she's the wife of Solomon.
"I am the Shulamite Girl," she says.
"And not only that," lifting her voice
like a tin cup, "I know for a fact
I am the bride of Christ."

The doctor shifts his clipboard
to the other knee. His pale assistant
shoots some liquid into other liquid
with a hypodermic, trying not to listen.
"Twenty-four years ago,"
the Shulamite Girl goes on,
"they locked me in a little cell.
No one came except my son.
When I got out after a year
with those crazy people, I told them
I was still the Shulamite Girl
and they locked me up again."

The doctor has a mind like the wood floor.
Her voice makes sharp, irritating sounds
upon it. After a few more
sentences he focuses behind her:
the hundred little cloudy amber vials
surrounding them like well-wishers,
the rolltop desk heaped with disheveled files
of other schizophrenics;
he watches a private plane scrape
the green hills like a razor,
his eyes wander to the charts, the mauve drapes—
there is no remedy for the Shulamite Girl.

You hover at the brink of nonexistence
with your soul-destroying love,
recalling the trees of frankincense,
the poetry of spices: saffron, myrrh, and cinnamon;
and after you've cross-referenced everything—
mandrakes and the names of cities—
you're still in the service of some abstract king
and you say of yourself, I am a wall,
knowing that even wrong dreams
might bear some benefits; as he has two
armies, you have the aquamarine
canopy of your belief.

BRENDA HILLMAN
Kensington, California

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Articles

Tort Reform and the Obstetric Access Crisis
The Case of the WAMI States

ROGER A. ROSENBLATT, MD, MPH, *Seattle, Washington;* RANDALL R. BOVBJERG, *Washington, DC;* AMANDA WHELAN, MA, *South Glamorgan, Wales; and* LAURA-MAE BALDWIN, MD, MPH; L. GARY HART, PhD; *and* CONSTANCE LONG, MA, *Seattle, Washington.*

The states of Washington, Alaska, Montana, and Idaho (WAMI) have all had declines in the proportion of physicians offering obstetric services during the past few years, a decline precipitated by rising medical malpractice premiums. One response to the problem of rising liability premiums has been the passage of extensive tort reform legislation. We present the results of recent studies of physicians' obstetric practices in the WAMI states and summarize the major changes in tort legislation and regulation that have occurred in these states.

Most general and family physicians in the WAMI region no longer provide obstetric care; by contrast, more than 80% of the obstetrician-gynecologists in the WAMI states are still practicing obstetrics. Despite the fact that only a minority of family physicians are still active in obstetrics, most rural family physicians in all four states still deliver babies. Most physicians in all four states limit the amount of care they provide to those covered by Medicaid, which suggests that significant barriers to care exist for medically indigent persons.

All four states have adopted significant tort reforms. Despite these changes in the legal environment, the cost of malpractice premiums and concerns over the likelihood of being sued continue to limit the number of physicians willing to provide obstetric care. Although it cannot be inferred from these data that tort reform has decreased the rate at which physicians give up obstetric practice, the evidence is compatible with such a conclusion.

(Rosenblatt RA, Bovbjerg RR, Whelan A, Baldwin LM, Hart LG, Long C: Tort reform and the obstetric access crisis—The case of the WAMI states. West J Med 1991 Jun; 154:693-699)

Obstetrics has been one of the aspects of medical practice most affected by provider responses to changes in the medical malpractice environment. During the 1980s, thousands of providers stopped practicing obstetrics or severely limited the scope of their practices, most frequently citing their concerns about medical malpractice as the reason for these changes in their obstetric practices.[1-5] Two groups have been severely affected by these changes in practice patterns: poor women who cannot afford to purchase care in the private market and women living in rural areas where obstetric care has become unavailable.[6-8] Problems of access to obstetric care have become major challenges to state government in all the states of the Pacific Northwest.

Washington, Alaska, Montana, and Idaho (the WAMI states) are large western states with dispersed rural populations. Each of these states has experienced an exodus of obstetric providers, with a major cause being identified as the obstetric malpractice crisis.[9-11] Although the prevailing tort laws have an effect on a wide variety of persons and organizations—from the school raising funds by hosting a summer carnival to the municipality trying to insure its swimming pool—the effect on obstetric care has been both poignant and highly visible.

As in most other states in the country, the four WAMI states instituted a series of legislative reforms at least partly motivated by the desire to restore the availability of obstetric care to rural populations. Although these legislative changes had much wider import than just their effect on obstetricians, family physicians, and midwives, the professional groups that provide virtually all obstetric care, the behavior of these groups may serve as an indicator of the efficacy of the tort changes. Because each state adopts its own legislative approach to tort reform, it may also be possible to determine the relative efficacy of these approaches by looking at end points such as the proportion of eligible practitioners who continue to practice obstetrics.

This study is a descriptive attempt to do such an analysis in the four WAMI states. We compare recent survey data about obstetric practice patterns of physicians in each state and juxtapose these findings with the major legislative reforms in tort law that have occurred over the past 20 years.

Methods

Legislation on Medical Malpractice

The legislative response to the malpractice crises of the 1970s and 1980s spanned three separate areas of law and regulation: reforms of the professional liability insurance industry, reforms aimed at improving the quality of medical care, and reforms of the tort system itself.[12] These legislative interventions were extremely diverse; they included such measures as the establishment of joint underwriting associations, designed to make malpractice insurance available, and limits on the amount of damages that could be awarded in cases where physicians or others were found to be negligent.

From the Department of Family Medicine, University of Washington School of Medicine, Seattle, Washington (Drs Rosenblatt, Baldwin, and Hart and Ms Long); The Urban Institute, Washington, DC (Mr Bovbjerg); and University of Wales College of Medicine, South Glamorgan, Wales (Ms Whelan).

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Reprint requests to Roger A. Rosenblatt, MD, MPH, Department of Family Medicine, HQ-30, University of Washington, Seattle, WA 98195.

TABLE 1.—*The Major Legal Reforms of the 1970s and 1980s**

- Insurance Reforms
  - Joint underwriting associations
  - Limits on insurance cancellation
  - Mandates for liability coverage
  - Patient compensation funds
  - Reporting requirements
- Reforms Aimed at Medical Quality
  - Peer review requirements, protection from lawsuits
  - Increased powers of disciplinary boards
  - Reporting requirements, data compilation
  - Requirements for continuing medical education
- Tort Reforms
  - Aimed at the number of lawsuits (insurance frequency)
    - Arbitration
    - Attorney fee controls
    - Certificate of merit
    - Costs awardable
    - Pretrial screening panels
    - Statutes of limitations
  - Aimed at size of recoveries (insurance severity)
    - *Ad domnums* restricted
    - Caps on awards (noneconomic, total)
    - Collateral source offset (permissive, mandatory)
    - Joint and several liability changes
    - Periodic payments of damages (structured awards)
    - Punitive damage limits
  - Aimed at plaintiffs' difficulty (or costs) of winning
    - Expert witness requirements
    - Informed consent limits
    - Professional standard of care reasserted
    - *Res ipso loquitur* restrictions
    - Statute of frauds for medical promises
  - Aimed at functioning, cost of judicial process
    - Mediation
    - Notice of intent to sue
    - Precalendar conference required
    - Preferred scheduling for malpractice cases
  - Miscellaneous
    - Extension of "Good Samaritan" statutes
    - Immunity for school athletic injuries
    - All other

*Adapted from Bovbjerg.[13]

To analyze these changes, we used categories developed as part of a national study of medical malpractice insurance (Table 1).[13]

Our research draws on this comprehensive review of the legislative record. Each legislative enactment for the four WAMI states was reviewed and characterized according to category. This statutory compilation was cross-checked against other listings distributed by trade associations and other sources. Because the original national survey of tort reform on which this article draws was concluded in 1987, more recent legislative enactments were documented by calling medical associations in the WAMI states. Any subsequent judicial invalidations or modifications of the original statues are also noted, as well as any termination of legislation in the case of predetermined "sunset" language in the original bills.

Obstetric Practice Patterns of WAMI Providers

Data on the obstetric activities of physicians in the four WAMI states were obtained from surveys of practicing physicians. In all four states, periodic surveys were initiated in the mid-1980s when it became apparent that a substantial number of physicians were deciding to discontinue obstetric practice. In each state, a different group was responsible for the survey. The sources of the survey material are summarized briefly on a state-by-state basis.

Washington. The Washington data are based on a 1989 survey of all potential obstetric care professionals in the state, including obstetricians, general and family physicians, and nurse midwives.[14] The data in this article are based on the responses of 1,407 physicians, representing a 73% response rate.

Alaska. The Alaska data come from two surveys conducted by the Department of Health and Social Services of the State of Alaska. The first questionnaire, which concentrated on the availability of obstetric care to low-income women, was sent to all potential obstetric care professionals in the summer of 1988 and had a 93% response rate (182 of the 196 physicians surveyed). These data were supplemented by a February 1989 survey that focused specifically on problems relating to medical liability.

Montana. The Montana data come from a 1988 survey of all Montana physician providers conducted by the Montana Academy of Family Practice. This was the most recent of a series of surveys conducted annually since 1985, when the obstetric care availability crisis was first noticed in Montana.

Idaho. The Idaho data are based on a survey administered jointly by the WAMI Rural Health Research Center and the Idaho Medical Association. The survey technique was identical to that used in the Washington study, and the questionnaire was mailed in the summer of 1989. There was a 77% response rate, with 303 physicians responding.

Analysis of Surveys

Because the surveys were undertaken by different groups, the data collected across the four states are not directly comparable. An attempt was made to ensure comparability of two key variables: differences between rural and urban provision of care and the relative propensity of physicians to provide obstetric care for medically indigent women. Differences in survey design, however, make it impossible to be sure that the categories were exactly equivalent.

The designation of rural and urban places was difficult, both because the existing federal definitions have limitations and because the concept of "rural" differs from one state to another. Although our final distinction was somewhat arbitrary, we tried to use categories that were meaningful in terms of the provision of medical care.

In Washington State, a county was considered rural if 50% or fewer of the inhabitants lived in an urban area as defined by the US Bureau of the Census; urban counties were those in which more than 50% of the inhabitants lived in urbanized areas. Thus, 19 counties were urban and 20 were rural.

In Alaska, physicians living in the Anchorage metropolitan area were considered to be urban; the rest of the state was classified as rural. In Montana, Billings and Cascade (Great Falls) counties were categorized as urban, and the rest of the counties were termed rural. In Idaho, only Ada County (Boise) was considered urban, and the rest of the state was considered rural. This recognizes the fact that, with the exception of Washington, there are few truly urban areas in the WAMI states.

Results

In the tables that follow, information was not uniformly available for all states or across all categories. Only data that were felt to be comparable are shown in the tables.

Table 2 displays the medical malpractice legislation enacted in the four WAMI states between 1955 and 1989. The

pattern in the WAMI states is similar to that which prevailed across the nation. Legislators in all four states selected from a variety of options, enacting a diverse array of legislation over more than three decades covered in this review. Statutory interventions covered all three major areas of reform: insurance, quality review, and alterations in tort law.

It is worth commenting briefly on each of these three broad areas to compare the case of the WAMI states with the national experience.

Reforms of Insurance

The WAMI states were similar to most other states in establishing legislation that permitted joint underwriting associations. A major response to the insurance availability crisis of the 1970s, joint underwriting associations established a mechanism whereby states could guarantee that most physicians could purchase insurance. Despite their statutory approval, only in Alaska did a state-sponsored insurance mechanism become the dominant malpractice insurer. Washington resembles many other states in its creation of a physician-sponsored medical malpractice insurance company that dominates the local market; 55% to 60% of all American physicians are now insured by such companies.[11]

The WAMI states differ from other states in that none of them limited the ability of insurance companies to cancel insurance coverage or established patient compensation funds. In all four states, the most important response to the lack of availability of insurance was to create mechanisms by which insurance coverage could be made available through nontraditional insurers.

Reforms Aimed at Medical Quality

The WAMI states directly mirrored the national experience in providing reforms aimed at medical quality. All four states enacted legislation protecting the peer review process, greatly increased the power of professional disciplinary boards, and expanded reporting requirements designed to record information about any disciplinary action taken against physicians. With one exception—the new reporting requirement in Washington—all of these legislative mandates occurred before 1980 and were unconnected with the crisis of insurance affordability that dominated the 1980s.

Reforms of Tort Law

All four states enacted legislation in the 1980s that sought to modify existing tort law. Although it is impossible in the space available to comment on all the elements of each state's laws, several approaches were common to most of the WAMI states.

Pretrial screening panels were enacted during the 1970s in all the states except Washington. Because these panels did not prevent the subsequent problem of malpractice insurance affordability, it might be reasonably concluded that this mechanism did not have much effect on the number or size of suits brought against physicians. By the same token, statutes of limitation were made narrower in all four states during the 1970s, although the Washington limitation was made even more restrictive with enactment of a major tort reform package in 1986. Again, the actual monetary consequence of this modification appears to have been minor.

The most far-reaching tort modifications were designed to limit the amount of recoveries. All four states instituted "strong" tort reform in the 1980s, with the core of each being a series of interrelated measures whose major effect was expected to be a decrease in the ultimate size of awards.

All four states restricted the use of *ad damnums*, the practice in which plaintiffs list the particular amount of award sought in the initial legal pleading. A much more important reform was a cap on awards, which was enacted in all of the states except Montana. This cap was subsequently struck down as unconstitutional by the Washington State Supreme Court in the case of *Sophie v Fibreboard*, thus removing one of the central pillars of the 1986 Washington State tort reform package. The cap was substantially weakened in Alaska where an exception was allowed for plaintiffs who suffered significant physical impairment. All four states also enacted changes in the doctrine of joint and several liability, thus eliminating to some extent the plaintiff's ability to recover disproportionately from "deep pockets" in cases of injury.

Two other tort reforms completed the package: arrangement for the periodic payment of damages and limitations on the amount of punitive damage. The first was instituted in all states except Montana, with limits on punitive damages introduced in all states but Washington. To date, these provisions still stand in each state where they were enacted. Although various other changes have been enacted, none of them are as pervasive or far-reaching as the ones mentioned.

The major finding illustrated in Table 2 is that the WAMI states, like their national counterparts, had two distinct periods of legislative activism with regard to medical malpractice legislation. The first took place during the 1970s in response to the problem of insurance availability; it was designed to make it easier for alternative insurance arrangements to be established and tightened up the surveillance of physicians but, for the most part, avoided meaningful reform of the tort process. The second wave occurred in 1986 and 1987 in response to skyrocketing medical malpractice insurance premiums, which translated into decreased availability of physician services and coincided with the barriers faced by many other private and public organizations in buying liability insurance to cover themselves against routine acts and services. This second wave focused on relatively strong measures, the intent of which was to make it more difficult to sue and recover large awards. All four of the WAMI states selected from the same package of reforms, and, with the exception of the Washington State caps, those reforms enacted are still operational.

Obstetric Practice Patterns

The obstetric access crisis of the late 1980s was triggered by the decision of many family physicians to discontinue obstetric practice. Although family practitioners deliver fewer babies in the aggregate than their obstetrician colleagues, approximately three times as many family physicians practice obstetrics as do obstetricians in the four WAMI states. In addition, for many of the rural communities in the northwestern states, family physicians are the only local source of obstetric care. Thus, the decision of large numbers of individual practitioners to stop delivering babies had an immediate effect on one of the basic health services taken for granted in many smaller communities.

Table 3 shows the current status of obstetric practice in all four states. The proportion of family physicians actively involved in obstetrics at the time of the surveys ranges from 53% in Idaho to 37% in Alaska. By contrast, a large majority

TABLE 2.—*Selected Changes in Tort-Related Legislation by WAMI State, 1955 to 1989*

Type of Enactment	*Washington*	*Alaska*	*Montana*	*Idaho*
Reforms of Insurance				
Joint underwriting associations (JUAs)	None; but insurance commissioner mandated to study effectiveness of JUAs (1986)	Medical Indemnity Corp of Alaska created (1976); in 1989, it insured 60% of all physicians and all but 2 rural hospitals in state	Montana Insurance Assistance Plan created (1977); 1979 amendment extended life of program to 1981; 1985 enactment provided for expiration in October 1991; JUA is on standby status	Hospital mutual or trust allowed; JUA created on standby status (1977); amended 1975 to no later than 1980; amended 1979 to no later than 1982
Mandates for liability coverage	Health care coverage subject to authority of state insurance commissioner; guidelines for assessing impact of mandatorily offered health coverage (1984)			
Reporting requirements, insurance cancellation limits			Insurers must report to insurance commissioner number of insureds, premiums paid, number and amount of claims made, lawsuits filed, settled, and pending, judgments rendered; no cancellation allowed based on claim for damages determined to be unfounded and no payment made by insurer (1971)	Before cancelling policy, must notify insureds 60 days in advance (1987)
Reforms Aimed at Medical Quality				
Peer review requirements, protection from lawsuits	Immunity from civil suit arising from duties on professional review committees (1969, amended 1976, 1985)	Peer review immunity unless information false and known to be false (1976)	Immune from liability for actions taken within scope of functions of committee if without malice; proceedings not discoverable or admissible into evidence in any other proceeding unless otherwise admissible (1975, 1977)	In-hospital staff committee and medical society: all records confidential and privileged; no civil liability for furnishing information or opinions to such committee; exception permits limited disclosure of information to malpractice claimant (1973)
Powers of disciplinary boards increased	Board given power to investigate charges of malpractice (1975); given additional staff (1979); medical discipline account in state treasury created (1983) (statute enacted 1955; amended 1975, 1979, 1982)	Board may impose sanctions for extensive list of violations: false advertising, demonstrated unfitness, unprofessional conduct, denied care if patient refuses to arbitrate, has lost license in another state, secured license through deceit (1974, amended 1983)	State Board of Medical Examiners has power to discipline physicians; amendment in 1975 added suspension or revocation of license in another jurisdiction to grounds for disciplinary action (1969; amended 1975, 1977, 1979)	Board of Professional Discipline can fire employees, promulgate rules and regulations, compel production of physicians and testimony of witnesses, control physician licensure, and has budgetary authority (1977)
New reporting requirements	Licensed health care professionals are required to report to Medical Disciplinary Board when they have personal knowledge that practicing physician has committed an act of unprofessional conduct (1986)	Hospitals required to report denial of staff privileges; doctors report treatment for alcohol or drug abuse or mental illness posing danger to public (1974)	Physicians must report incompetence or unprofessional conduct; physician's insurer must report any claim of professional negligence and disposition of claim to State Board of Medical Examiners; hospitals must report changes in staff privileges (1977)	Hospital must report changes in hospital staff privileges, any disciplinary action taken against physician (1976)
Requirements for continuing medical education	Washington State Board of Medical Examiners created, 1961 (1955 legislature); power to demand continuing medical education (1971)	Continuing medical education mandated as prescribed by regulation, no less than 15 hours in 5 years (1976)		
Risk management		For licensing, hospital must have internal program to investigate frequency and causes of malpractice incidents, develop and implement measures to reduce risks of injury to patients, and analyze patient grievances relating to patient care (1976)		
Tort Reforms Aimed at Number ("Frequency") of Lawsuits				
Arbitration		Arbitration framework; both before- and after-injury arbitration allowed (1967; amended 1976, 1978)		
Attorney fee controls	Court review of reasonableness of attorney fees required (1976)	Attorney fees may only be awarded if action is contested without trial or fully contested as determined by the court (1962, amended 1986)		Limited to 40% of value recoverable, court review of fees' reasonableness required in all malpractice cases (1975)
Costs awardable		1962 statute does not specify which costs are awardable; attorney fees awardable if action is contested without trial or is fully contested, as determined by court (1986)		
		malpractice actions (if deemed necessary for expertise); panel's report is discoverable and admissible as evidence; if ruled that party made a frivolous claim or defense, that party pays all expert panel's costs (1976)	is subject to a valid arbitration agreement; panel investigates whether claim merits a trial; decision is not binding (1977)	immune from civil process; no record kept of proceedings, evidence is returned at end; has subpoena power; unanimous decision on damage amount may be told to parties, insurers, and other third-party payers; panel decision not appealable; panel members not paid, 90-day hearing limit (1976)
Statutes of limitation	Malpractice action must be brought within 3 years of negligence or 1 year of discovery, in no event longer than 8 years from the act (1971; amended 1976, 1986)	Basic tort/personal injury statute of limitation of 2 years (1962)	Malpractice action must be brought within 3 years of injury or discovery, with maximum of 5 years (1971)	Action must be brought within 2 years following injury or 1 year after discovery (1970); 1971 amendment to generic statute of limitations added provision that for medical or professional malpractice before 1971, generic law was applicable
Aimed at Size ("Severity") of Recoveries				
Ad damnums restricted	*Ad damnum* clause 4.28.360	Lawsuits can plead only that damages demanded are within jurisdiction of court (1976)	No dollar amount allowed in pleadings (1977)	Grounds for mistrial if any person discloses amount of general damages sued for to the jury (1976)
Caps on awards (noneconomic, total)	Limitation on noneconomic damages (1986); struck down as unconstitutional (1989)	Limit of $500,000 per separate incident for personal injury based on negligence (1986); plaintiffs with physical impairment or disfigurement excepted		$400,000 cap on noneconomic losses (1987)
Collateral source rule		Evidence of collateral sources is admissible after fact finder has rendered an award; claimant can only receive damages in excess of amounts received as compensation for injuries from collateral sources (1976)	Plaintiff allowed to introduce premium payments (1987)	Damages limited to compensatory damages not previously paid or satisfied by any other person or from any other source (1975)
Joint and several liability changes	1981 Act codified doctrine of joint and several liability; amended 1986	A party who is allocated less than 50% of the total fault may not be jointly liable for more than twice the percentage of fault allocated to that party (1986); joint and several liability eliminated as of March 9, 1989	Joint liability eliminated in cases where party's negligence is 50% or less of total; that person severally liable only (1987)	Repeal of joint and several liability (1987)
Periodic payment of damages	Future damages in excess of $100,000 may be paid periodically; however, noneconomic damages must be paid at outset (1986)	Medical malpractice statute that court may enforce a detailed payment structure enacted (1976); generic statute enacted (1986)		Either party may elect to have future damages over $100,000 paid in periodic payments (1987)
Punitive damage limits		May not be awarded unless supported by clear and convincing evidence (1986)	Awarded only where actual fraud or malice; no dollar limit (1987)	Special court hearing before filing to determine if claim for punitive damages is warranted (1987)
Aimed at Plaintiffs' Difficulty (or Costs) of Winning				
Advance payment	Advance payment not admissible before judgment; jury cannot draw inference of liability therefrom (1976)	Advance payment not admissible; jury cannot draw inference of liability; excess payments not refundable to defendant (1976)	Advance payment not admissible; jury cannot draw inference of liability; excess payments not refundable to defendant (1973)	
Informed consent limits		Patient must show physician has failed to disclose common risks and reasonable alternatives of proposed intervention (1976)		Standard of disclosure set by professional custom; person who in good faith receives consent to a procedure is immune from liability (1975)
Professional standard of care reasserted	Injury must result from failure to follow accepted standard of care (1976)	Professional standard of care applied to all medical services (1976)		Professional standard of care applied to all medical services, emergency department services, generalists, and specialists (1976)
Res ipsa loquitur restrictions		Doctrine prohibited; no presumption of negligence in medical malpractice because injury alone does not imply presence of negligence (1967, amended 1976)		
Statute of frauds for medical promises		No claim against health care provider for breach of oral contract to cure or achieve specific result (1976)		
Miscellaneous				
Extension of "Good Samaritan" statutes		Enacted 1974; amended to cover any person responding to emergency (1976, 1978, 1986)		No liability for refraining from helping in an emergency situation (1973)
Other	Limited liability for nonprofit officials (1986)			

TABLE 3.—*Physicians' Obstetrical Practice Patterns in Four WAMI States by Specialty*

State (Year of Survey) and Specialty	Percent Doing Obstetrics	Respondents, No.
Washington (1989)		
FP/GP	46	1,002
Ob/Gyn	80	359
Alaska (1988)		
FP/GP	37	141
Ob/Gyn	76	37
Montana (1988)		
FP/GP	48	130
Ob/Gyn	95	37
Idaho (1989)		
FP/GP	53	249
Ob/Gyn	96	54

FP/GP = family and general practice, Ob/Gyn = obstetrics and gynecology

of obstetricians continue to practice obstetrics, ranging from 96% in Idaho to 76% in Alaska. We know from earlier studies that the number and proportion of family physicians practicing obstetrics have declined in all four states.[9-11,15]

The propensity to practice obstetrics differs notably from rural to urban areas, as seen in Table 4. In every state, rural family physicians are much more likely than their urban counterparts to practice obstetrics. In all four states, most rural family physicians practice obstetrics, and most urban family physicians do not.

Although obstetricians follow the same pattern, the distinction between urban and rural practitioners is much less pronounced. The only state in which a substantial number of obstetricians no longer practice obstetrics is Washington, where 70 urban obstetricians who responded to our survey reported that they had given up obstetrics. This number exceeds the total of all other obstetricians in the four states who report they no longer practice obstetrics.

In addition to women living in rural areas, the other major population segment affected by the decline in the availability of obstetric practitioners has been the medically indigent, represented in this study by patients enrolled in the Medicaid program. Table 5 shows the policies adopted by active obstetric practitioners in three of the four states toward Medicaid-supported women as reported on the surveys. Although data were unavailable for Montana, the returns from the three other states show a pattern considerably more disparate than was seen with respect to the decision to practice obstetrics at all. In all three states, family physicians reported that they are more likely than obstetricians to accept an unlimited number of Medicaid patients. In Alaska, however, by far most of both types of providers stated that they will take all Medicaid patients, a decision opposite to that in Washington and Idaho. In these two states, most physicians limit the number of Medicaid patients they will accept. Few practitioners in any location responded that they provide no care to Medicaid women.

Discussion

There are many similarities across the four states in this study, with respect to both problems of obstetric access and the legislative responses to these problems. Although these are cross-sectional data, we know from anecdotal information and previous studies that before the past five years most family physicians—and virtually all obstetricians—incorporated obstetrics into their practices.[16] Yet this study shows that a minority of family physicians now continue to actively practice obstetrics, particularly in urban areas. Given the dependence of rural communities on family physicians for routine obstetric care, this pattern explains the widespread concern about the availability of that care in these states.

The data are remarkably similar for the four states. As in other studies, physicians reported that issues related to medical malpractice are the most powerful factors influencing their collective decisions to continue basic practice.[2,15] The cost of medical malpractice insurance is the most important factor, often exceeding the fiscal capacity of family physicians, who usually have relatively few obstetric patients, to continue to offer this service. To this economic decision is added the difficult-to-quantify—but no less important—emotional effects of a climate in which obstetric malpractice suits are perceived as increasingly common and increasingly expensive.

These data also suggest that there may be problems in ensuring that medically indigent persons receive ready access to obstetric care. Although substantial differences exist among the three states for which we have data, most of the physicians in these surveys ration care to medically indigent persons, a finding similar to that of other studies.[8] The impression from these surveys is that the care of medically indigent patients tends to fall on the shoulders of a subset of the physician population. If these relatively few physicians make the decision to quit practicing obstetrics, the availabil-

TABLE 4.—*Percentage of Physicians Currently Practicing Obstetrics by Specialty and by Urban or Rural Designation in Four WAMI States*

State (Year of Survey) and Specialty	Percent Doing Obstetrics		Respondents, No.	
	Rural	Urban	Rural	Urban
Washington (1989)				
FP/GP	64	43	845	154
Ob/Gyn	95	79	334	22
Alaska (1988)				
FP/GP	51	18	60	81
Ob/Gyn	83	72	25	12
Montana (1988)				
FP/GP	54	17	12	123
Ob/Gyn	96	100	14	24
Idaho (1989)				
FP/GP	57	35	40	208
Ob/Gyn	97	94	16	38

FP/GP = family and general practice, Ob/Gyn = obstetrics and gynecology

TABLE 5.—*Current Policy Toward Medicaid Patients by Obstetric Physicians in 3 WAMI States**

State (Year of Survey) and Specialty	Physicians, %			No. of Respondents
	Unlimited No. of Medicaid Patients	No Care to Medicaid Patients	Limit No. of Medicaid Patients	
Washington (1989)				
FP/GP	34	7	59	442
Ob/Gyn	21	8	71	273
Alaska (1988)				
FP/GP	85	10	5	52
Ob/Gyn	79	14	7	28
Idaho (1989)				
FP/GP	45	12	43	120
Ob/Gyn	30	10	60	50

FP/GP = family and general practice, Ob/Gyn = obstetrics and gynecology

*Based on physicians' own estimates.

ity of obstetric care to this vulnerable part of the population may decrease rapidly and possibly catastrophically.

Although we do not attempt to link the declining availability of obstetric practitioners directly with legislative modifications of tort and insurance law, the review of legislation shows that all four states enacted "strong" tort reforms at about the same time that declining obstetric care availability became a major political issue in the Pacific Northwest and Alaska. The reforms are remarkably similar across all four states, relying for the most part on legislative changes designed to make it more difficult for plaintiffs to prevail and less lucrative when they do win a jury verdict.

The similarity of the legislative changes makes it difficult to link any particular legislative strategy with any particular effect on provider behavior. It is clear from these surveys that a substantial number of obstetrically trained physicians remain outside the obstetric work force. Other sources of information make it evident that all four states still consider themselves to be in the midst of a crisis of obstetric availability, largely due to the reluctance of providers to either practice obstetrics at all or provide it to certain segments of the population.

Should we conclude from these data that tort reform has been a failure? Or has the concern over medical malpractice issues been a red herring, invoked by physicians who choose to discontinue obstetric practice for unrelated reasons that they are less willing to disclose? Although both of these hypotheses may ultimately prove to have some merit, it is too early to conclude that tort reform has not succeeded.

The insurance cycle in medical malpractice is relatively long and is affected not only by the legal fabric but by the investment climate. The cost of medical malpractice insurance is affected only in part by the prevailing laws, and changes in law may require many years before they will affect the reserve and premium responses of insurance companies.

In addition, the modification in tort law may have prevented an even more pervasive crisis. Anecdotal reports suggest that, at least in Washington State, there has been some stabilization of provider supply, and this may be the case in the other states as well.[14] The enactment of California's Medical Insurance Compensation Reform Act—first passed in 1975 and ruled constitutional in 1985—has been credited by that state's medical underwriters as the primary reason that medical malpractice premiums have moderated in that state.[17] Changes in tort law are probably less likely to affect current practitioners—who may be reluctant to attempt to return to practicing obstetrics after a hiatus of several years—than future practitioners. Thus, we will need more time to draw firm conclusions.

The four WAMI states have confronted similar problems and have responded to these problems in a similar way. These data suggest that there may be some value in adopting a regional approach to the resolution of these issues. Certainly, pooling data about obstetric practice, legislative changes, and medical malpractice experience seems to have value for all the states. Given the fact that many of the problems are shared, it is likely that solutions will also be effective beyond the borders of individual northwestern states.

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Conferences and Reviews

Genetics of Colon Cancer

DENNIS J. AHNEN, MD, *Denver, Colorado*

Strikingly rapid advances in the identification of genetic events that are important in colonic carcinogenesis have been made in the past several years. Specific inherited (adenomatous polyposis coli gene) and acquired (*ras* gene point mutations; c-*myc* gene amplification; allelic deletion at specific sites on chromosomes 5, 17, and 18) genetic abnormalities appear to be capable of mediating steps in the progression from normal to malignant colonic mucosa. Understanding these genetic factors and how they influence cellular function will have a profound effect on medical practice. High-risk populations will be (and are being) identified by genetic markers, thus allowing prevention and screening to be more precisely targeted to the population at risk; intervention strategies will be designed on the basis of the known cellular defects of neoplastic colonic mucosa; and new molecular preventive and therapeutic approaches can be developed.

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Major advances have occurred in the past few years in the understanding of genetic factors related to colonic carcinogenesis. The population genetics of inherited colon cancer syndromes, such as familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer, provided the initial evidence that genetic factors could determine the risk of large bowel cancer, and subsequent studies have highlighted the importance of hereditary factors in the risk of sporadic colorectal cancer. Molecular genetic studies have identified the location of the gene responsible for familial adenomatous polyposis and several other specific genes or genetic sites that appear to be important in the progression from normal colonic mucosa to colon cancer. These advances have already been applied clinically to identify carriers for the familial adenomatous polyposis gene, and they have the potential to revolutionize the way we approach the prevention and treatment of cancer of the colon.

Population Genetics

Inherited Colon Cancer Syndromes

The rare inherited colon cancer syndromes are all inherited in an autosomal dominant pattern with nearly 100% penetrance. They are divided into the adenomatous polyposis coli (APC) syndrome, which accounts for about 1% of the total number of colon cancers, and the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, which is about five times more common.

Adenomatous polyposis coli. The two major types of APC syndromes—familial adenomatous polyposis and Gardner's syndrome—have been separated on clinical grounds. Both clinical syndromes are characterized by the appearance of thousands of adenomas of the colon. The coexistence of multiple benign extraintestinal tumors in Gardner's syndrome have separated it from familial adenomatous polyposis. Affected patients with these syndromes have inherited an adenoma gene, and one or more of the adenomas invariably progress to colon cancer. The gene responsible for familial polyposis has now been localized by linkage analysis in several laboratories to the long arm of chromosome number 5 (Figure 1)[1-4] at a site called the APC locus. Patients with Gardner's syndrome show a similar linkage to the APC locus, and, thus, this syndrome is due to inheritance of either a different APC allele or a closely linked gene. These observations have made it possible to use genetic markers to identify APC gene carriers with kindreds and thus to determine those family members who require screening and those who do not. This genetic marker is now being used to simplify prevention programs in families with familial colon cancers.

Although several laboratories are attempting to sequence the APC gene, it has not yet been identified, and the function of the gene product is not known. Because an increased proliferative rate and an expansion of the proliferative compartment are the earliest alterations seen in the colonic mucosa of patients with familial polyposis coli, it has been suggested that the gene may play a role in regulating colon cell growth. Erisman and co-workers have put forth the hypothesis that the APC gene product results in deregulated overexpression of the c-*myc* gene product (see Molecular Genetics section).[4] Understanding the function of this gene product will provide important insight into familial adenomatous polyposis and the cellular mechanisms responsible for adenoma formation in the APC syndromes and in sporadic colorectal adenomas.

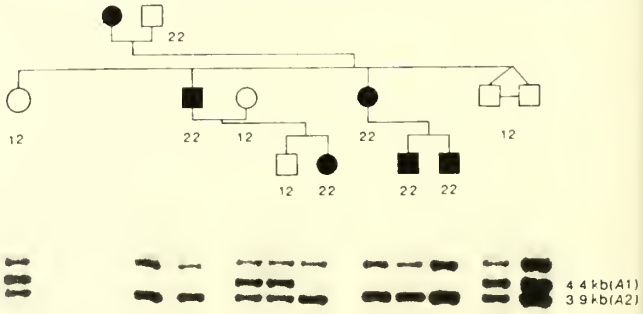

Figure 1.—Pedigree of a family with familial adenomatous polyposis shows segregation of the phenotype **(darkened symbols)** with a 3.9-kilobase fragment on the long arm of chromosome 5 (from Bodmer et al[1]).

From the Department of Medicine, University of Colorado School of Medicine, and the Gastroenterology Section, Veterans Administration Medical Center, Denver.
Reprint requests to Dennis J. Ahnen, MD, Chief, Gastroenterology Section, VA Medical Center 111E, 1055 Clermont St, Denver, CO 80220.

ABBREVIATIONS USED IN TEXT

APC = adenomatous polyposis coli
GTP = guanosine triphosphate
GTPase = guanosine triphosphatase
HNPCC = hereditary nonpolyposis colorectal carcinoma
mRNA = messenger RNA

Hereditary nonpolyposis colorectal cancer. The HNPCC syndromes are characterized by the inheritance of a cancer gene rather than an adenoma gene. Cancers in this syndrome are thought to develop in adenomas, but only one or a few adenomas are seen. The adenomas in this disorder, however, have a high propensity to progress to colonic cancer. Two HNPCC syndromes have been described: The site-specific colon cancer syndrome is characterized by only an increased colon cancer risk, whereas the cancer family syndrome is associated with an increased risk for colon, uterine, ovarian, breast, and other cancers.[5] The HNPCC syndromes are more difficult to identify with certainty because of the lack of a clear phenotypic marker such as polyposis. Hereditary nonpolyposis colorectal cancer must be suspected by the clinical features of the cancer—young age of occurrence, often multiple, often proximal—and the autosomal dominant inheritance pattern. Neither the gene locus (loci) nor the function of the gene product(s) responsible for these syndromes is known for certain, but Lynch and colleagues have reported linkage of the cancer family phenotype to the Kidd blood group,[6] which is located on the long arm of chromosome 18. This location is interesting because of the high frequency (80%) of allelic deletion on the long arm of chromosome 18 in patients with sporadic large bowel cancer (see section on Molecular Genetics).

Sporadic Colon Cancer

There is no doubt that environmental factors are important in determining the risk for sporadic colon cancer, but genetic influences appear to play a role as well. A family history of colon cancer has long been known to be a risk factor for sporadic colon cancer.[7] Recently Cannon-Albright and associates have suggested that an autosomal dominantly inherited gene may predispose to a susceptibility to the environmental factors that cause colon cancer.[8] They identified 34 kindreds in which one or two members had colonic neoplasia. They did flexible sigmoidoscopy on 407 relatives from these kindreds and 263 of the relatives' spouses as controls. Adenomas were found significantly more often in the relatives (19%) than in the spouses (12%). When Cannon-Albright and co-workers analyzed the results by pedigree analysis (Figure 2), they concluded that the data were most consistent with the inheritance of an autosomal dominant gene with a calculated gene frequency of about 20% and a penetrance of about 60% by age 80. If this analysis is correct, they calculated that nearly all of the risk for colon cancer could be accounted for by gene carriers. If this is true, it would be justifiable to use powerful screening tools (colonoscopy) and to design specific dietary intervention strategies for known gene carriers.

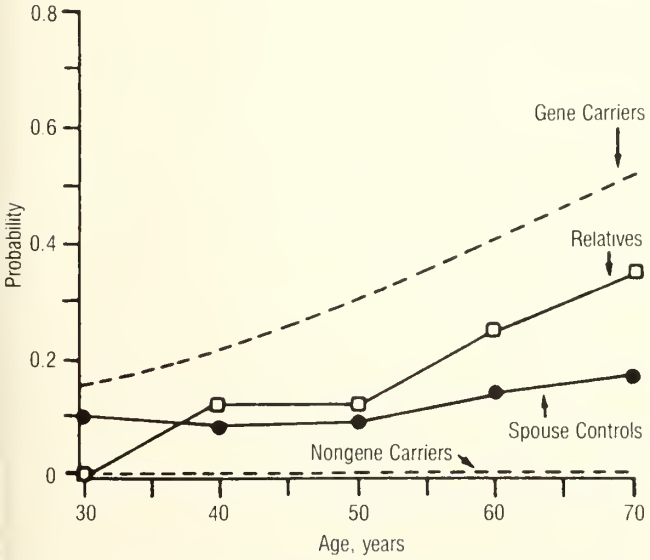

Figure 2.—The observed frequency of adenomatous polyps **(solid lines)** is shown among relatives of probands with colonic cancer or adenomas and spouse controls and the predicted frequency of adenomatous polyps **(dashed lines)** among carriers and noncarriers of the susceptibility allele (from Cannon-Albright et al[8]).

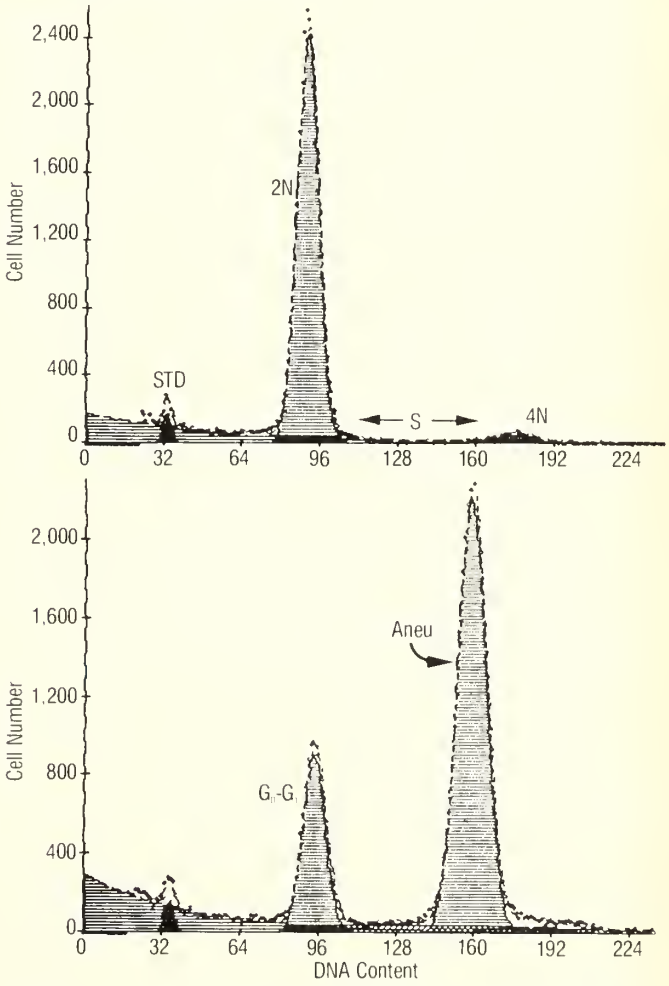

Figure 3.—Flow cytometric analysis of the DNA content of colonoscopic biopsy specimens from patients with inflammatory bowel disease show the cell number plotted on the vertical axis and the intensity of fluorescence (DNA content) plotted on the horizontal axis. **Top,** In this normal histogram, a major population of cells is found to have 2N DNA (two copies of each chromosome) compared with the internal standard peak (**STD** [chicken erythrocytes]). The 2N cells are in the G_0 and G_1 phase of the cell cycle. A smaller population of cells with 4N DNA represents cells that have completed DNA synthesis but have not yet divided. These cells are in the G_2 or M phase of the cell cycle. Cells that are synthesizing DNA (in the S phase) are present in the region between the G_0-G_1 and G_2-M peaks. **Bottom,** In this histogram, an aneuploid population **(arrow)** is seen as a distinct peak of cells separate from the G_0-G_1 or G_2-M peak.

TABLE 1.—*Prognostic Significance of Ploidy Status in Colon Cancer*

Reference	Patients, No.	Tissue	Location	Aneuploid, %	Percent Survival (Yrs of Follow-up) Diploid	Aneuploid	P Value for Survival Differences	Significance Independent of Stage
Wiggers et al, 1988[18]	279	Archival	Colon/rectum	58	80	70(4)	<.05	Yes
Quirke et al, 1986[21]	125	Archival	Rectal	54	57	35(5)	.02	Not tested
Schutte et al, 1987[13]	121	Archival	Rectosigmoid	46	65	42(5)	.01	Yes
Scott et al, 1987[12]	279	Archival	Colon/rectum	62	75	65(4)	.07	In C only
Quirke et al, 1987[11]	264	Archival	Colon/rectum	52	64	50(5)	.17	Yes
Enblad et al, 1987[14]	166	Fresh	Rectosigmoid	75	80	58(5)	>.05	No
Emdin et al, 1987[15]	37	Fresh	Colon/rectum	62	69	40(3)	.007	Yes
Rognum et al, 1987[16]	100	Fresh	Colon/rectum	63	64	49(5)	>.05	No
Jones et al, 1988[17]	123	Fresh	Colon/rectum	67	64	34(3)	.007	In B only

Molecular Genetics

Profound abnormalities of DNA have been identified in adenomatous polyps and cancer of the large bowel. The spectrum of genetic abnormalities ranges from gross quantitative changes in DNA content, as seen by flow cytometric analysis of DNA content, through deletions of specific chromosomal segments to single-point mutation in the *ras* gene.

Aneuploidy

Aneuploidy is defined as an abnormal amount of DNA. Aneuploid cell populations can be rapidly and reliably identified using flow cytometric analysis of DNA content. In this technique, isolated nuclei from the tissue of interest are prepared and incubated with a fluorescent dye that binds quantitatively to DNA. The flow cytometer quantitates the amount of fluorescence, a measure of DNA content, in each nucleus and plots the cumulative data in a histogram. Aneuploid populations appear as a distinct peak of cells separate from the normal cells in the G_0 or G_1 phase of the cell cycle that contain two copies of each chromosome (2N DNA) and the cells in G_2 and M phases that contain 4N DNA (Figure 3).

Aneuploidy occurs in a fraction of cancers of many types, and in patients with breast cancer and those with lymphoma, aneuploidy is a poor prognostic sign. About 60% of colon cancers are aneuploid, and, in general, patients with aneuploid tumors have a higher recurrence rate and a poorer survival than those with diploid tumors (Figure 4, Table 1).[9-19] It is not yet certain whether aneuploidy is an independent prognostic variable after correcting for stage and histologic differentiation, but some studies suggest it is.[9,16]

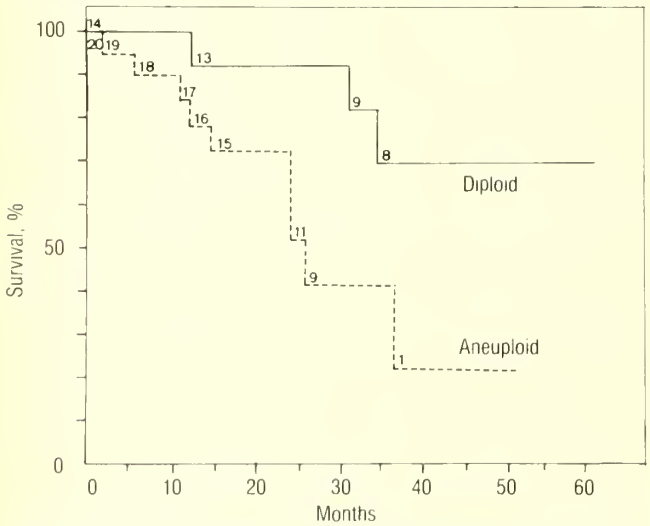

Figure 4.—Survival curves of patients with diploid colon cancer show a survival advantage over those with aneuploid cancer (from Emdin et al[15]).

Aneuploidy was originally thought to occur only in patients with malignant neoplasms, but it is now clear that it is seen in some histologically benign-appearing neoplasms such as adenomatous polyps[21,22] and in nonneoplastic colonic mucosa of some patients with ulcerative colitis.[23] It is not yet known if the presence of aneuploidy in patients with these clinical conditions is predictive of an increased risk of the subsequent development of dysplasia or carcinoma.

Proto-oncogenes

Proto-oncogenes are normal cellular genes that when activated can cause the dysregulation of normal growth and differentiation and enhance the probability of neoplastic transformation. Proto-oncogenes can be activated through point mutation, resulting in an abnormal gene product or an abnormally high (unregulated) expression of the normal gene product. It is thought that the activation of only one allele of an oncogene is necessary to facilitate transformation—that is, the activated gene acts in a dominant manner. Several lines of evidence—reviewed by Friend and co-workers[24] and Chan and McGee[25]—have established that oncogenes are important in human carcinogenesis. Initial studies of retroviral carcinogenesis established that several normal cellular genes had become incorporated into the retroviral genome. In most cases, these genes were activated in the retrovirus by point mutation so that they were capable of inducing malignant transformation on viral infection of cells in culture. The importance of the retroviral oncogenes was reinforced when many of the same activated genes were found to be the transforming genes isolated in transfection experiments with DNA from cancer cell lines and fresh specimens of human cancer. Subsequently, cytogenetic studies have shown that translocations characteristic of certain tumors result in the increased expression of specific proto-oncogenes, and studies of animals have shown that chemical carcinogens can result in the activation of some of these same genes through point mutation.

More than 40 different oncogenes have been identified: They can be divided into several groups on the basis of their cellular location and function. Many of the oncogene products have structural homology to soluble growth factors (*sis* with platelet-derived growth factor, *int*-2 with fibroblast growth factor) and transmembrane growth factor receptors (*erb* B and *neu* with epidermal growth factor receptors, *fms* with colony-stimulating factor receptor). A large group of oncogenes code for nuclear proteins—*myc*, *fos*, *myb*, p53—whose function is as yet unknown, although it is tempting to suggest that such proteins might regulate proliferation at the transcriptional level. Another large group of oncogenes code for intracellular protein kinases that have tyrosine (*src*, *abl*,

fes, yes) or serine-threonine *(mos, raf)* phosphorylase activity. Finally, some oncogenes code for proteins located at the inner surface of the plasma membrane (the *ras* family).

Alterations in the expression of two oncogenes (*myc* and *ras*) have been reported in human colon cancers. The *myc* gene is located on chromosome 8 and codes for a 62,000 molecular weight protein that is located predominantly in the nucleus. The function of the *myc* gene product is not yet known, but it is thought to be involved in regulating cellular proliferation. An enhanced expression due to gene amplification and translocation is the major mechanism of *myc* gene activation reported in human neoplasia. In patients with colon cancer, *myc* gene amplification has been seen in a small number,[26-28] and enhanced (deregulated) expression of the *myc* messenger RNA (mRNA) and gene product is found in most (about 70%) colon cancers.[29-33]

As mentioned, an association between the allelic deletion of the APC gene locus and an overexpression of the c-*myc* gene has been reported in colon cancers.[4] Erisman and colleagues found that none of eight colon cancers with normal levels of c-*myc* mRNA had an allelic deletion of chromosome 5q (the site of the APC gene), whereas 5q deletion was seen in 9 of 19 colon cancers in which the c-*myc* mRNA was overexpressed. Whether there is a causal relationship between the APC gene product and c-*myc* regulation deserves further investigation. Thus far, deregulation of the c-*myc* gene does not correlate with histologic differentiation, Dukes stage, ploidy status, or survival. It is not yet known whether an increased *myc* expression is primary and mediates one of the steps in malignant transformation or is merely secondary to an increased fraction of cycling cells in the malignant tissue. Thus, the specific role, if any, of the c-*myc* gene in colon cancer is not yet defined.

It does appear that activation of the K-*ras* oncogene is important in colonic neoplasia. The *ras* family of oncogenes codes for 21,000 molecular weight proteins that share many properties with the G proteins that are known to play a role in the signal transduction pathway from membrane-bound receptors to adenylate cyclase.[34] Like the G proteins, the *ras* gene products are anchored to the inner surface of the plasma membrane, they can bind guanosine triphosphate (GTP) and guanosine diphosphate, and they have intrinsic guanosine triphosphatase (GTPase) activity. An increased expression of *ras* oncogene mRNA is seen in adenomas and colon cancers, but, as with the *myc* gene, the clinical importance of increased expression alone is not clear.[35,36]

Point mutation in the K-*ras* gene has been found in about 40% of colonic adenomas and carcinomas.[37-39] Nearly all of the K-*ras* point mutations in colonic neoplasia are located in codon 12, and it is known that mutations in this codon inhibit the GTPase activity of the *ras* gene product. For other G proteins, it is known that GTP binding results in activation of the G protein and that hydrolysis of the bound GTP by the intrinsic GTPase terminates the activated state. Extending the analogy between G proteins and the *ras* gene to their function would suggest that the *ras* proteins function in the signal transduction pathway of cell surface receptors to cellular targets and that the loss of GTPase activity through point mutation will result in a continuously activated protein. The cell thus acts as if it is continually exposed to the ligand (?growth factor). This hypothesis is yet to be proved directly, and thus far neither the putative receptors nor the cellular targets related to the *ras* proteins have been defined.

The finding that point mutation in the *ras* gene occurs in only about 40% of patients with colon cancer suggests that this specific genetic abnormality is not essential for colonic carcinogenesis and that there is more than one set of genetic events that can result in colonic cancer. The observation that point mutation in the *ras* gene occurs as frequently in adenomas as in carcinomas suggests that it may mediate one of the earlier steps in colonic carcinogenesis, perhaps in the evolution from nonneoplastic to adenomatous mucosa.

Understanding the oncogene-induced alterations in cellular mechanisms will allow the transition from the current therapeutic empiricism to more rational approaches to cancer prevention and therapy. Designing drugs to correct the known cellular abnormalities is an appealing approach suggested by this recent work.

Tumor Suppressor Genes

Tumor suppressor genes are normal cellular genes that suppress carcinogenesis in some manner. The original suggestions that such genes existed came from studies with somatic cell hybrids which clearly showed that when malignant cells were fused with normal cells, the resulting hybrid cells were nontumorigenic. This phenomenon of tumor suppression indicated that a gene (or genes) from a normal cell could overcome a defective function in a malignant cell and reimpose the normal growth responses. The loss of the function of such tumor suppressor genes is thought to cause dysregulation of normal growth and differentiation and enhance the probability of a neoplastic transformation.[24] It is thought that loss of the function of both alleles of a tumor suppressor gene is usually required for the facilitation of transformation, although this has not been proved for most of the putative tumor suppressor genes. An allele could be inactivated by several mechanisms—deletion, point mutation, methylation—but allelic deletion is the most easily detected of these alterations. Possible sites of putative tumor suppressor genes for colon cancer have been identified by observing consistent loci of allelic deletion in the tumors compared with the normal colonic mucosa. Allelic deletion can be recognized by taking advantage of the heterogeneity in the DNA sequences of the two copies of each chromosome. This heterogeneity in sequence results in the appearance of different-sized fragments of DNA from the two chromosomes when they are cleaved with restriction enzymes. The DNA fragments can be separated on the basis of size by electrophoresis, and the fragments containing a specific genetic locus can be identified by incubation with radiolabeled probes for the locus. As shown in Figure 5, allelic deletion of a specific genetic locus in cancer can be recognized by comparing the restriction fragment pattern of the tumor with that of the normal colonic mucosa.

Allelic deletions have been found in every chromosome in at least a few colon cancers, and many of these are probably epiphenomena of the tumor itself.[40] Deletion at three genetic sites, however—the long arm of chromosomes 5 and 18, the short arm of chromosome 17—does appear to be important in colon cancer.

Chromosome 5 deletion. The allelic deletion on the long arm of chromosome 5 is interesting because it is at the same site (5q22) as the adenomatous polyposis coli gene. The finding of deletion at this site in about 30% to 40% of patients with colonic adenomas and carcinomas[39,41,42] suggests that

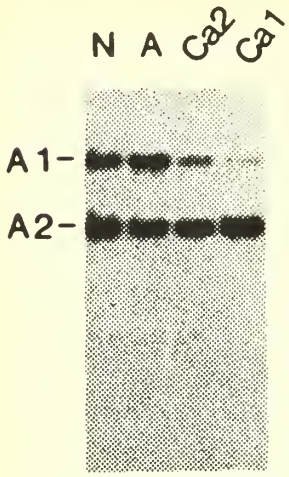

Figure 5.—There is a loss of heterozygosity of a site on the long arm of chromosome 5 in colorectal carcinomas from a patient with familial polyposis. In the normal colon **(N)** and in adenomatous mucosa **(A)**, 2 alleles (A1 and A2) are seen. In 2 carcinomas (Ca2 and Ca1), the intensity of A1 is greatly decreased compared with A2, indicating loss of the A2 alleles in the cancers (from Okamoto et al[42]).

this locus is relevant to sporadic colon cancer and the rare genetic syndromes. If the APC gene is, in fact, a tumor suppressor gene that requires inactivation of both alleles to facilitate transformation, the most simple hypothesis for its role in colon cancer is that in APC, one inactive gene is inherited and the other undergoes somatic mutation, whereas both alleles are inactivated by somatic mutation in sporadic colon cancer. This mechanism has been established for the retinoblastoma gene.[43] This hypothesis may be an oversimplification for APC, however. If the adenoma is considered the result of the inactivation of both APC alleles, then the somatic mutation at the APC site would have to occur in thousands of separate sites in the colon because thousands of separate adenomas develop in this syndrome. Such a frequency, while possible, would suggest that the inherited defect predisposes the remaining allele to somatic mutation. If the cancer is considered to be the result of inactivation of both alleles, then the loss of a single allele must be capable of facilitating neoplastic progression to the stage of an adenoma and inactivation of both alleles is not necessary for some effects of the putative tumor suppressor gene. The function of the APC gene is not yet known, although, as mentioned, a role in regulating the c-*myc* gene has been suggested.[4] The observations that the gene is important in the polyposis syndromes and that deletion at this site is found about as frequently in adenomas as in carcinomas suggest that it may mediate one of the early steps in colonic carcinogenesis, perhaps in the development of adenomas. Although the finding of deletion at this site in only 20% to 40% of colonic neoplasms may mean that genetic alteration at this site is not required for colonic carcinogenesis, it must be remembered that allelic deletions are gross genetic abnormalities. When the gene itself is identified and characterized, it will be possible to determine if more subtle alterations (point mutation, smaller deletions, methylation) also occur at this site.

Chromosome 18 deletion. Allelic deletion of a site on the long arm of chromosome 18 (18q21–qter) occurs in about 10% of colonic adenomas and about 75% of colon cancers.[39] A putative tumor suppressor gene (the DCC [deleted in colorectal carcinomas] gene) at this site has been partially cloned and sequenced. The DCC gene shows significant homology to normal cell adhesion molecules and other cell surface glycoproteins, and it is tempting to speculate that the DCC gene product normally mediates cell surface interactions and that its loss might disrupt normal cell interactions. A deletion at this site in only a small fraction of adenomas and a much higher fraction of cancers suggests that this site may be important in the progression of adenomas to carcinomas.

Chromosome 17 deletion. The site of the allelic deletions on the short arm of chromosome 17 has been more extensively characterized than any of the others. Such deletions occur in about 5% of patients with colonic adenomas, 45% of patients with colonic adenomas that were associated with focally invasive carcinomas, and 75% of those with established colon cancers.[39] Baker and associates looked at this site more closely and found that the deletions in colonic cancers occur at the site of the p53 gene (17p12p13.3), a previously described gene that was originally thought to be an oncogene.[44] The same group has examined the p53 coding region of the remaining allele in several of the colon cancer patients found to have deletion of one 17p allele. In each case they found a somatic mutation in the remaining allele. These observations strongly suggest that the p53 gene is relevant to colon cancer.

The p53 gene encodes for a 53,000 molecular weight nuclear protein of unknown function. This protein was originally found to be associated with the large T antigen in SV-40 transformed cells; the implication was that the gene was a transforming gene. Studies showing that point-mutated p53, like the *myc* oncogene, can mediate transformation when transfected in combination with the K-*ras* oncogene into rat embryo fibroblasts, which further suggested a role for p53 as an oncogene. Its deletion in colon cancers, however, is more consistent with a tumor-suppressor function for p53, and the observed somatic mutations allele could be the mechanism of inactivation of the remaining allele. From the evidence thus

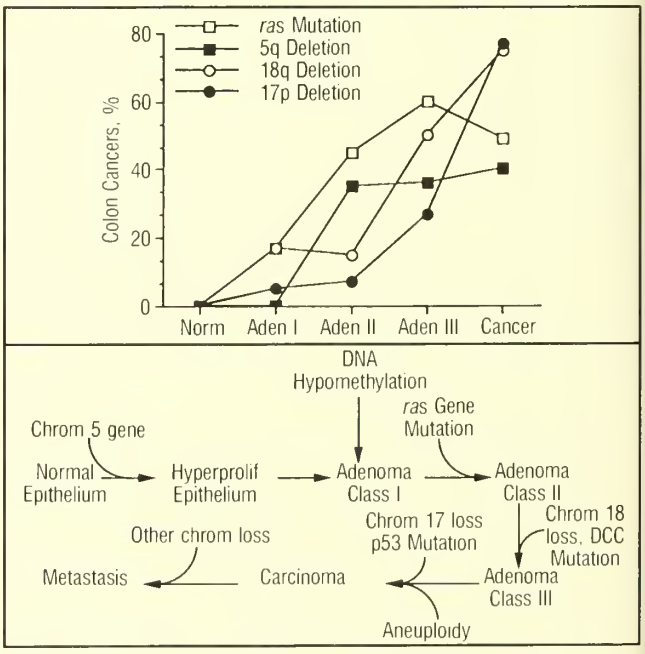

Figure 6.—Top, The relative frequency of four specific genetic events is shown in normal colonic mucosa (Norm), small adenomas from patients with familial adenomatous polyposis (Aden I), larger adenomas (Aden II), the adenomatous portions of adenomas with focally invasive cancer (Aden III), and colon cancers. The *ras* point mutation and deletion at the familial adenomatous polyposis site on chromosome 5q occur with similar frequency in the larger adenomas and cancers, whereas deletions on chromosomes 17 and 18 occur more frequently in the cancers than in the adenomas. **Bottom,** A conceptual framework is shown for the possible relationship of genetic events to the several steps of colonic carcinogenesis (modified from Vogelstein et al[39]).

far, it is not yet clear if the p53 gene is acting in colon cancer as a dominant tumor suppressor gene, with functional inactivation of both alleles (one by deletion and one by somatic mutation), as a dominant-acting oncogene activated by somatic mutation (this seems the least likely as there would be no need for allelic deletion to produce this effect), or both (the activated gene functioning unopposed because of deletion of the other allele).[45]

It is likely that other oncogenes or tumor suppressor genes will be found to mediate other steps in colonic carcinogenesis, but other types of genetic regulation such as DNA methylation could play a role as well. In general, the DNA of inactive genes tends to be more heavily methylated than the DNA of active genes. The observation of pronounced hypomethylation in colonic adenomas compared with either normal mucosa or colon cancers suggests the possibility that the mechanism of gene regulation could be important in the adenomatous stage of colonic cancer. Vogelstein and co-workers have presented a conceptual framework of these genetic events suggesting that the chromosome 5 deletion and the *ras* point mutation might occur early during colonic carcinogenesis, with the chromosome 17 and 18 deletions occurring later (Figure 6).[39] This framework highlights the likely importance of multiple mutations in colonic carcinogenesis but is not meant to imply that the events need to occur in the sequence shown, nor that other genetic or epigenetic events are not involved.

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Conferences and Reviews

Lyme Disease

DANIEL W. RAHN, MD, *and* STEPHEN E. MALAWISTA, MD, *New Haven, Connecticut*

Lyme disease is a tick-borne immune-mediated inflammatory disorder caused by a newly recognized spirochete, *Borrelia burgdorferi.* Over the past 15 years it has progressed from a medical curiosity to the most frequently recognized vector-borne illness in the United States. Its clinical hallmark is an early expanding skin lesion, erythema chronicum migrans, that may be followed weeks to months later by a spectrum of systemic features with joint, neurologic, and cardiac abnormalities predominating. The clinical manifestations are protean; symptoms may refer to any involved organ system alone or in combination. All stages of Lyme disease may respond to antibiotics, but treatment of early disease is the most successful. Although cases of the illness are concentrated in certain endemic areas, foci of Lyme disease are widely distributed within the United States and Europe.

History

Lyme arthritis was recognized in November 1975 because of an unusual geographic cluster of children with inflammatory arthropathy in the region of Lyme, Connecticut.[1] Its early elucidation—natural history,[1-6] immunopathogenesis,[7-11] epidemiology,[12-15] pathology,[2,4,11] and therapy[16-19]—was carried out primarily at Yale University by Steere and Malawista and their colleagues. It soon became clear that this was a multisystem disorder (Lyme disease[2-6]) occurring at any age, in both sexes, and often preceded by a characteristic expanding skin lesion, erythema chronicum migrans (ECM). Recognition of this skin lesion provided an important link to disorders previously recognized in Europe. Erythema chronicum migrans had been described in 1909[20] and subsequently connected with the bite of the sheep tick, *Ixodes ricinus,*[21] and with tick-borne meningopolyneuritis.[22,23] These syndromes are now often subsumed under the name, Lyme disease. In the Lyme region, a closely related deer tick, *Ixodes dammini* (a member of the so-called *Ixodes ricinus* complex), was implicated as the principal disease vector on epidemiologic grounds.[12-15]

In 1982, Burgdorfer and associates[24] isolated the spirochete that bears his name from *I dammini* collected on Shelter Island, New York, and linked it serologically to patients with Lyme disease. Within months this organism had been cultured from specimens of blood, skin, and cerebrospinal fluid of patients, and specific IgM and IgG antibody responses had been delineated.[25,26] Because of its infectious cause but inflammatory or "rheumatic" expression, Lyme disease, beyond intrinsic interest as a new nosologic entity, presents a unique human model for an infectious cause of a chronic rheumatic disease.[27]

Pathogenesis

By morphology, physiology, and DNA composition, the spirochetes found in tick vectors and in patients with Lyme disease have been classified as *Borrelia* rather than *Leptospira* or *Treponema*, the other two spirochetes pathogenic for man. Clinical isolates in the United States and Europe have to date all belonged to a single species: *Borrelia burgdorferi.*[28] Unlike pathogenic treponemes, however, *B burgdorferi* can be cultured in artificial media in vitro. This organism is also responsible for some cases of an early skin lesion, benign lymphocytoma,[29] and for a late one, acrodermatitis chronica atrophicans (ACA),[29,30] both seen at present primarily in Europe.

Characterization of clinical isolates has revealed several immunodominant proteins expressed during human infection; these include a flagellar antigen and two outer surface proteins, ospA and ospB.[31-33] The antigenic reactivities of outer surface proteins may differ among isolates and can vary with serial passages of a single isolate in vitro.[34] European isolates have been more heterogeneous than American ones, particularly with respect to ospA. Molecular weights and immunoreactivity of ospB have differed among both American and European isolates.[35] Variation in protein composition could eventually explain differences in the clinical expression of Lyme disease in Europe and America. Compared with American disease, *B burgdorferi* infection in Europe is characterized by milder but more prolonged early disease, less frequent occurrence of multiple skin lesions and arthritis, and more frequent occurrence of meningoradiculitis and ACA.

Continuous cultivation of *B burgdorferi* in vitro results in a loss of pathogenicity as evidenced by its inability to infect the white-footed mouse, *Peromyscus leucopus*, the primary reservoir of *B burgdorferi* in the wild in the northeastern United States. This change occurred after 11 to 15 serial passages and was associated with the disappearance of ospB from the surface of the organism.[34] Similar alterations in the expression of surface proteins may occur during human infection,[36] which could explain how the organism evades immunologic destruction in the presence of a mature immune response.

Recovery of *B burgdorferi* is straightforward from the tick vector (see below) but generally difficult from patients, in part because of a relative paucity of organisms in most clinical specimens. An exception is its isolation from biopsy specimens of ECM cultured in improved media: for example, 6 of 14 in one study[37]; 9 of 13 in another.[30] Nevertheless, positive cultures have been reported at all stages of the illness—from blood (early),[25,26,38] secondary annular lesions,[30] meningitic

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From the Department of Internal Medicine, Section of Rheumatology, Yale University School of Medicine, New Haven, Connecticut.
Reprint requests to Daniel W. Rahn, MD, Dept of Internal Medicine, Section of Rheumatology, Yale Univ School of Medicine, 333 Cedar St, New Haven, CT 06510.

ABBREVIATIONS USED IN TEXT

ACA = acrodermatitis chronica atrophicans
ECM = erythema chronicum migrans
ELISA = enzyme-linked immunosorbent assay

cerebrospinal fluid,[25] heart,[39] joint fluid,[40] and even from an ACA lesion that had been present for more than ten years.[30] Spirochetes have also been identified by silver stain or by immunofluorescence in some histologic sections of ECM[41] and rarely of secondary annular lesions,[42] synovium,[43] brain,[44,45] eye,[46] heart,[47] striated muscle,[48] liver,[49] spleen, kidney, and bone marrow.[50]

From these data, considered in the context of the clinical and epidemiologic features of Lyme disease (see below), the following pathogenetic sequence can be proposed. *Borrelia burgdorferi* is transmitted to the skin of the parasitized host by the tick vector. After an incubation period,[6] the spirochetes migrate outward in the skin (causing ECM), spread in lymph (regional adenopathy), or disseminate in blood to other skin sites (secondary annular lesions) or organs (central nervous system, joints, heart, and presumably liver, spleen, and kidney). Maternal-fetal transmission has occurred but appears to be distinctly uncommon.[50,51] Although organisms are hard to find in later stages of Lyme disease, it is likely that live spirochetes are driving the illness throughout its course. Evidence for this interpretation includes the responsiveness of many patients to antibiotics; the rare sightings of spirochetes in affected tissues and fluids; possibly the antigen-specific proliferation of lymphocytes from these fluids[52,53]; and an expansion of the antibody response to additional spirochetal antigens over time.[36]

Lyme disease is associated with characteristic immune abnormalities.[7-10] At disease onset (ECM), most patients have evidence of circulating immune complexes.[9,10] At that time, the findings of elevated serum IgM levels and cryoglobulins containing IgM predict subsequent nervous system, heart, or joint involvement[7,8]; that is, early humoral findings have prognostic significance. Serial determinations of serum IgM can be a helpful laboratory indicator of risk of future disease activity. These abnormalities tend to persist during neurologic or cardiac involvement, but by the time arthritis is present, serum IgM levels are more often normal. By then, immune complexes are usually lacking in serum but are present uniformly in joint fluid,[10] where their titers correlate positively with the local concentration of polymorphonuclear leukocytes.[54] Mononuclear cells from peripheral blood show increasing proliferative responses to spirochetal antigens as the disease progresses, but the greatest reactivity is seen in synovial fluid cells from inflamed joints.[52] Mononuclear cells exposed to spirochetes produce interleukin-1, and interleukin-1 has been found in fluid from inflamed joints.[55] On biopsy a proliferative synovium is seen, often replete with lymphocytes and plasma cells that presumably are capable of producing immunoglobulin locally. Thus, an initially disseminated, immune-mediated inflammatory disorder becomes in some patients localized and propagated in joints.

In addition to factors related to the pathogenicity of specific isolates of *B burgdorferi*, immunogenetic makeup may play a role in whether infected persons are able to rid themselves of spirochetes. Patients with chronic arthritis have been reported to have an increased frequency of the B-cell alloantigens DR4 and sometimes DR3[56] or DR2,[57] and persons with another late manifestation, ACA, have an increased frequency of DR2.[58]

Epidemiology

Lyme disease is the most commonly reported vector-transmitted disease in the United States and has essentially worldwide distribution. In the United States, there are three distinct foci: the Northeast, from Massachusetts to Maryland; the upper Midwest, in Wisconsin and Minnesota; and the West, in coastal California and Oregon.[14,59] The illness, however, has been reported to occur in 43 states, as well as throughout Europe, Asia, and in Australia.[59,60] The earliest known cases in the United States occurred on Cape Cod in 1962 and in Lyme, Connecticut, in 1965[14]; reported cases in the US now exceed 13,000.[60] Lyme disease can occur at any age and in either sex.[15] The onset of illness is generally between May 1 and November 30; the peak is in June and July.[6]

The primary vectors of Lyme disease are tiny hard ticks of the *Ixodes ricinus* complex. Major foci of disease correspond to the distribution of *I dammini* (Northeast and Midwest),[14,59] *Ixodes pacificus* (West),[14,59] *I ricinus* (Europe and western USSR),[59,61] and *Ixodes persulcatus* (Japan, China, and Asian parts of USSR).[61,62] Lyme disease, however, occurs in Australia despite the absence of ixodid ticks.[63] Other vectors, including the Lone Star tick, *Amblyomma americanum*, are likely in some areas of the United States.[64,65] Biting insects have been proposed as possible secondary vectors, but evidence to support transmission of disease by them is lacking.[66] The rising incidence of Lyme disease in recent years in the United States may be explained by multiple factors, including an increase in the number of ixodid ticks, the outward migration of residential areas into previously rural woodlands (habitats favored by ixodid ticks and their hosts), an exploding deer population, and increased recognition.

Study of the two-year life cycle of *I dammini*, the eastern deer tick, helps explain the ecology of *B burgdorferi* and the epidemiology of Lyme disease (Figure 1).[67,68] Adult female ticks, having gorged on a blood meal the preceding fall or winter (generally on deer, their preferred host), deposit as many as several thousand fertilized eggs in early spring. Larvae emerge six to eight weeks later and feed once for two days in mid- to late summer on a variety of small mammals or passerine birds, but preferentially on the white-footed mouse. After molting to nymphs the next spring, they ingest a second blood meal for three or more days in late spring or early summer. Unlike many ticks, nymphal *I dammini* are not at all fastidious in selecting a host; in addition to the preferred white-footed mouse, they are known to feed on a broad range of small mammals and birds.[69] After feeding, nymphs molt to adults later in the same season. Both adult males and females attach primarily to deer, but males probably do not feed; mating occurs while the females feed. Deer occupy a pivotal position in the ecology of Lyme disease because of the narrow host range of adult ixodid ticks; in one study on Great Island, Massachusetts, the number of *I dammini* ticks was reduced through the virtual elimination of deer.[70] Fertilized eggs are laid again the following spring and the cycle begins anew.[13,67,71] In one study in the United States, 31% of 314 patients with early Lyme disease recalled a tick bite at the skin site where ECM developed days to weeks later.[6] The six ticks that were saved and examined were all identified as nymphal *I dammini*, whose peak questing period occurs from

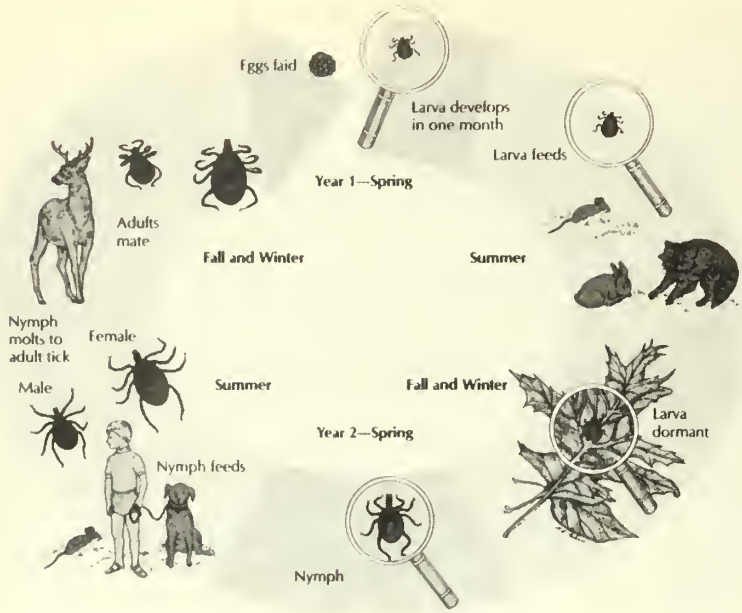

Figure 1.—The life cycle of *Ixodes dammini* spans 2 years. In the spring of the first year **(top)**, eggs hatch and larvae emerge. In the summer, the larvae feed once. They acquire *Borrelia burgdorferi*, the spirochete that causes Lyme disease, from their preferred host, the white-footed mouse. The next spring **(bottom)**, the larvae molt into nymphs, which feed once again. Again, mice are the preferred host; humans, to whom the ticks transmit Lyme disease, are not necessary for maintenance of the tick's life cycle. The nymphs molt into adults that mate while the female is feeding on a deer; eggs are laid the next spring and the cycle is repeated (from Rahn and Malawista[68]).

May through July. Subsequent epidemiologic studies have established nymphal ixodid ticks to be the stage primarily responsible for transmission of the causative spirochete.[67]

In areas endemic for Lyme disease, the incidence of *B burgdorferi* in nymphal *I dammini* ranges from about 20% to more than 60%, but the infection rate in larvae is much lower[24,25,65] (compare *I pacificus:* nymphs 0.9% to 2%[72]). Field studies have shown that ticks acquire spirochetes by feeding on a previously infected reservoir host, most commonly the white-footed mouse, which is almost universally infected with *B burgdorferi* in summer months.[73] Vertical transmission of the causative organism is rare both in ticks and in mice.[74] The establishment of an endemic focus therefore requires not only a tick vector in proximity with humans but also a reservoir host capable of becoming infected with *B burgdorferi* and of transmitting this agent to ticks. The low infection rate in *I pacificus* compared with *I dammini* may be explained by the preference of larvae and nymphs of this species for lizards rather than small rodents.[75] Lizards are not competent reservoirs for *B burgdorferi* and cannot transmit spirochetes to ticks that parasitize them.

Borrelia burgdorferi has been isolated, or specific antibody found, in blood or tissue specimens of a wide variety of large and small animals, including domestic dogs (which can develop arthritis) and birds.[76-80] Whether birds can function as reservoir hosts is currently disputed,[69,81] but they clearly may favor the spread of infection through the transport of infected ticks to new locales.

TABLE 1.—*Early Symptoms and Signs of Lyme Disease**

Symptoms	%	*Signs*	%
Malaise, fatigue, and lethargy	80	Erythema chronicum migrans	100†
Headache	64	Multiple annular lesions	48
Fever and chills	59	Lymphadenopathy	
Stiff neck	48	Regional	41
Arthralgias	48	Generalized	20
Myalgias	43	Pain on neck flexion	17
Backache	26	Malar rash	13
Anorexia	23	Erythematous throat	12
Sore throat	17	Conjunctivitis	11
Nausea	17	Right upper quadrant tenderness	8
Dysesthesia	11	Splenomegaly	6
Vomiting	10	Hepatomegaly	5
Abdominal pain	8	Muscle tenderness	4
Photophobia	6	Periorbital edema	3
Hand stiffness	5	Evanescent skin lesions	3
Dizziness	5	Abdominal tenderness	2
Cough	5	Testicular swelling	1
Chest pain	4		
Ear pain	4		
Diarrhea	2		

*These figures were derived from the study of 314 patients reported in Steere and Bartenhagen.[6]

†Erythema chronicum migrans was required for inclusion in this study

Clinical Characteristics

Lyme disease has been divided by convention into three clinical stages with considerable overlap (Table 1), but most patients do not exhibit all of them and, in fact, seroconversion can occur in asymptomatic persons.[82,83] The illness usually begins with ECM and associated symptoms (stage 1), sometimes followed weeks to months later by neurologic or cardiac abnormalities (stage 2) and weeks to years later by arthritis (stage 3). Chronic neurologic and skin involvement may occur years after disease onset.

Early Manifestations

Erythema chronicum migrans, the unique clinical marker for Lyme disease, begins as an erythematous macule or papule at the site where the tick vector had gorged.[2,6] The interval between tick bite and onset of ECM varies from 3 to 32 days.[6] The area of redness gradually expands to an average diameter of about 15 cm (range 3 to 68 cm). The outer borders are generally flat and without scale. There is usually partial central clearing, but centers may be red and indurated, vesicular, or even necrotic. Variations occur—many smaller rings within a single larger lesion, for example. The thigh, groin, and axilla are common sites. The lesion is warm to touch but not often sore or pruritic and easily missed if out of sight. Routine histologic findings are not specifically diagnostic and are compatible with an arthropod bite: a heavy dermal infiltrate of mononuclear cells, without epidermal change except at the site of the tick bite itself.

A few days after the onset of ECM, about half of the

patients in the United States have the development of multiple secondary lesions resulting from hematogenous spread of infection from a primary lesion. Secondary lesions resemble ECM itself but are generally smaller, migrate less, and lack indurated centers. Individual lesions may come and go, and their borders sometimes merge. (Benign lymphocytoma cutis, an erythematous papule at the site of a tick bite, usually on the nipple or ear lobe, has been reported as an early manifestation of infection in Europe.[29]) Erythema chronicum migrans and secondary lesions fade in three to four weeks (range, 1 day to 14 months) but may recur.

Skin involvement is often accompanied by flulike symptoms: malaise and fatigue, headache, stiff neck, fever and chills, myalgia, and arthralgia.[2,6] Some patients have evidence suggesting meningeal irritation with episodes of excruciating headache, neck pain, and stiffness typically varying over hours at this stage of the illness. Spinal fluid examination, which may reveal lymphocytic pleocytosis later in the illness, is typically normal during ECM, and objective neurologic deficits are lacking.[3]

Except for fatigue and lethargy, which are often constant, the signs and symptoms of early Lyme disease are typified by their intermittent and changing nature. For example, a patient may have meningitic attacks for several days, and then a few days of improvement, followed by the onset of migratory musculoskeletal pain. The pain may involve muscles and periarticular sites (tendons, bursae, and ligamentous attachments) as well as joints. Joint swelling is uncommon within the first few weeks of illness. The pain tends to affect only one or two sites at a time and to last a few hours to several days in a given location. The various systemic symptoms of early Lyme disease may precede ECM (or occur without it) and last for days to months (especially fatigue and lethargy) after the skin lesions have disappeared.

In Europe, untreated ECM more commonly has a prolonged course and less commonly is associated with multiple annular lesions or prominent systemic symptoms. Similarly, laboratory abnormalities and subsequent arthritis are less common in Europe than in the United States.[84]

Later Manifestations

Neurologic involvement. Within several weeks to months of disease onset (usually after ECM and associated symptoms have resolved), about 15% of patients in the United States will have neurologic abnormalities develop, including meningitis, encephalitis, chorea, cranial neuritis (including bilateral facial palsy), motor and sensory radiculoneuritis, mononeuritis multiplex, or diffuse peripheral sensorimotor neuropathy in various combinations.[3,85,86] A common pattern of neurologic involvement, occurring within the first few months of illness, is fluctuating meningoencephalitis, often with superimposed cranial nerve (particularly facial) palsy or peripheral radiculoneuropathy, but Bell's palsy may occur alone. After the first few weeks of illness, patients with meningitic symptoms have lymphocytic pleocytosis (averaging 0.001×10^6 per liter [100 cells per μl] in cerebrospinal fluid). *Borrelia burgdorferi* has been cultured from cerebrospinal fluid during meningitis.[25] Lyme meningitis is often accompanied by irritability, photophobia, and impaired concentration indicative of mild encephalitis, which may be reflected in diffuse slowing on electroencephalography. Although patients complain of neck stiffness, Kernig and Brudzinski signs are typically absent, as is the case with other nonpurulent meningitides. Neurologic abnormalities last for months but usually resolve completely even without antibiotic therapy; they may recur (late neurologic complications are noted later in the article).

Cardiac involvement. During the same stage of illness in which acute neurologic abnormalities occur, carditis develops in about 8% of patients in the United States, most often characterized by fluctuating atrioventricular (AV) block, which may vary rapidly from first-degree to Mobitz type 1 second-degree AV block (Wenckebach) or even complete heart block.[5] Less commonly, patients have evidence of more diffuse myopericarditis with electrocardiographic changes (ST-T wave changes and/or ventricular or supraventricular arrhythmias) and radionuclide evidence of left ventricular dysfunction or, rarely, frank cardiomegaly. Patients with Lyme carditis may seek medical attention because of unexplained syncope or presyncope or occasional complaints only of palpitations. Cardiac complaints may be the presenting manifestations of Lyme disease. Gallium scan-positive myocarditis[87] and, in one fatal case, spirochete-positive pancarditis[47] have been reported. One patient described recently had convincing evidence of diffuse myocarditis proved by culture of a specimen of myocardium obtained by transvenous endomyocardial biopsy. This was associated with longstanding congestive cardiomyopathy that did not reverse with antibiotic therapy.[39] No patients have had significant valvular involvement (compare acute rheumatic fever).[5] Cardiac involvement is usually brief, ranging from a few days to six weeks, and resolves in most patients even without specific antibiotic therapy.

Arthritis. Lyme arthritis, although the first recognized clinical manifestation of this illness, actually occurs relatively late in the course of the disease. Symptoms varying from migratory musculoskeletal pain to overt inflammatory arthritis develop from a few weeks to as long as two years after the onset of illness. About 60% of patients with Lyme disease eventually have frank arthritis[2,4,11] characterized by intermittent, asymmetric oligoarticular swelling and pain affecting primarily large joints, especially the knee. Both large and small joints may be affected, however, and a few patients have had symmetric polyarthritis.

A typical attack of Lyme arthritis begins with sudden swelling of the affected joint (usually one), often out of proportion to pain. When the knee is involved, as in 80% of cases, the swelling, because it often occurs in active young adults or children, is commonly initially attributed to trauma. Knee effusions may have volumes of 100 ml or more and lead to the formation of popliteal cysts (Baker's cysts) that may rupture. An attack of arthritis may last from a few days to months. Recurrences are frequent in the first year after onset; they decrease with time but may recur for years. Overall, attacks cease in 10% to 20% of patients per year.[88]

Fatigue commonly accompanies active joint involvement, but fever or other systemic symptoms are unusual at this stage. Joint fluid leukocyte counts have varied from 0.5 to 110×10^6 per liter (500 to 110,000 cells per μl), with an average of about 25 (25,000) cells, mostly polymorphonuclear leukocytes.[2] Total protein levels have ranged from 30 to 80 grams per liter (3 to 8 grams per dl) but are generally normal to mildly elevated. Joint fluid complement and glucose levels are usually normal. During Lyme arthritis, immune complexes are often concentrated in joint fluid and not increased in peripheral blood.[7-9]

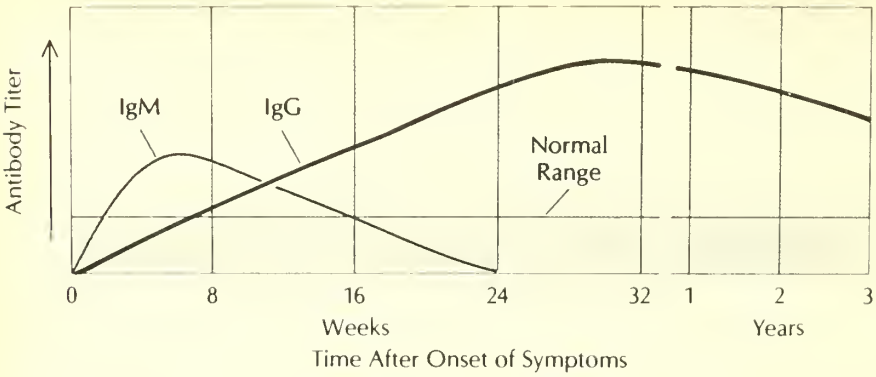

Figure 2.—The typical antibody response is shown in persons with untreated Lyme disease. Specific IgM antibodies usually become detectable 2 to 4 weeks after onset of disease. The subsequent appearance of specific IgG antibodies is frequently concurrent with systemic manifestations. IgM antibody levels typically decline over 4 to 6 months, even in untreated patients; a persistence of high IgM antibody levels is predictive of later manifestations of disease. IgG antibodies are almost always elevated during late disease (from Rahn and Malawista[68]).

In about 10% of patients with arthritis, large-joint involvement may become chronic, with pannus formation. Erosions of cartilage and bone and permanent joint disability have occurred in a minority of these patients.[4,11] Synovial histologic features have mimicked those of rheumatoid arthritis: surface deposits of fibrin, villous hypertrophy, vascular proliferation, and a heavy infiltration of mononuclear cells (T and B cells intermixed).[2,4,11] Rarely, there may be obliterative endarteritis with spirochetes in perivascular areas demonstrable by monoclonal antibody or silver staining.[43,89] Synovial biopsies have been performed primarily in those patients with more severe joint involvement so the pathology of the early lesion is less well characterized.

Borrelia burgdorferi potently stimulates mononuclear cells to produce interleukin-1. Levels of this lymphokine have been elevated in synovial fluids.[90] Synovium removed from one patient with chronic Lyme arthritis, when grown in tissue culture, produced large amounts of collagenase and prostaglandin E_2.[11] Thus, in chronic Lyme arthritis, the joint fluid cell counts, immune reactants (except for rheumatoid factor), synovial histology, amounts of synovial enzymes released, and resulting destruction of cartilage and bone may be similar to those in rheumatoid arthritis.

Radiographic findings in Lyme arthritis have varied according to the clinical picture.[91] Patients with intermittent arthritis have most often had only joint effusions, occasionally accompanied by periarticular soft tissue edema and enthesopathic changes, including even ossification of insertion sites of tendons and ligaments. Later changes in patients with chronic arthritis have included juxta-articular osteoporosis, cartilage loss, and marginal erosions. Fewer patients have had postinflammatory degenerative changes such as cartilage loss, subarticular sclerosis, and osteophyte formation.

Late Manifestations

Other late findings (years) associated with this infection include the chronic skin lesion, acrodermatitis chronica atrophicans,[29,30] well known in Europe but still rare in the United States. This is an infiltrated plaque or nodule, especially on an extensor surface, that may eventually become atrophic; the active lesions contain spirochetes.[30] There may be underlying joint changes affecting the same extremity as ACA.

Uncommon late chronic neurologic manifestations include a variety of lesions of the central and peripheral nervous system. Demyelinating encephalopathy with multiple white matter lesions seen on magnetic resonance imaging scan and a multiple sclerosis-like clinical picture have occurred rarely. The documentation for this disorder has included its occurrence in persons with a history of previous early Lyme disease, immunoreactivity against *B burgdorferi* in both serum and cerebrospinal fluid, and resolution following antibiotic therapy. It should be emphasized, however, that serologic and cerebrospinal fluid screening of patients from multiple sclerosis clinics in areas endemic for Lyme disease have not revealed any relationship, in general, between *B burgdorferi* infection and demyelinating disease.[92] The same may be said about *B burgdorferi* infection and amyotrophic lateral sclerosis.[93] A diffuse sensory neuropathy has also been described as a chronic manifestation of Lyme disease.[86] This lesion is described electrophysiologically as a mild axonal polyneuropathy. Symptoms have been limited to peripheral paresthesias; the evidence favoring a relationship of this lesion to *B burgdorferi* infection has consisted of both serologic data and response to antibiotic therapy. Transverse myelitis has also been reported to occur.[94,95] Mild memory impairment, subtle mood changes, and chronic fatigue states are under investigation as chronic neurologic syndromes.[95] "Progressive *Borrelia* encephalomyelitis"[96] is currently recognized more frequently in Europe than in the United States.

Laboratory Diagnosis

The diagnosis of Lyme disease is based on the recognition of clinical features of the illness in a patient with a history of possible exposure to the causative organism. Culture of *B burgdorferi* from patients is definitive but has rarely been successful except from skin biopsy specimens.[25,30,37] Recently the organism was isolated from blood in a significant minority of patients with systemic manifestations of early disease.[38] Special tissue-staining techniques[41-43,45] generally have a low yield and are not readily available.

Determination of specific antibody titers is currently the most helpful diagnostic test for Lyme disease. IgM antibodies against *B burgdorferi* usually appear two to four weeks after disease onset and reach a peak between the third and sixth week; specific IgG antibody titers rise more slowly and are generally highest months later when arthritis is present (Figure 2).[25,97] Persons with Lyme disease of more than six weeks' duration can be expected to have detectable specific antibodies. The tests used, however, are not yet standardized, and results from different commercial laboratories may vary.[98] Although either immunofluorescence assays or enzyme-linked immunosorbent assays (ELISA) are offered, the ELISA technique offers the advantages of being more reproducibile, less subjective, and automatable. Such assays, however, cannot distinguish patients with active infection from those with previous immunologic exposure but without current infection. In our experience, the vast majority of

persons with Lyme arthritis have a positive serologic response, and this finding makes antibody titers against *B burgdorferi* particularly useful in differentiating Lyme disease from other rheumatic syndromes, especially when ECM has been missed, forgotten, or absent. Antibodies against *B burgdorferi* can cross-react with other spirochetes, including *Treponema pallidum*, but patients with Lyme disease do not have positive VDRL tests.[6,97] False-positive results can also occur in patients with high-titer rheumatoid factors and during infectious mononucleosis. Currently Lyme serologic studies are frequently obtained in circumstances in which the risk of Lyme disease by clinical and epidemiologic criteria is slight. In this setting, when the pretest likelihood of disease being present is slight, a significant percentage of positive results will be falsely positive regardless of the specificity of the test. It is extremely important, therefore, to consider the clinical context when interpreting the result of a Lyme serologic study.

Positive T-cell blastogenic responses to *B burgdorferi* can suggest that the host has encountered the Lyme spirochete sometime in the past,[99] but their specificity is currently in question,[100] and patients with active disease usually have positive antibody titers.[99] Other tests under development seek to identify spirochetal material in host fluids or tissues. They include a test for spirochetal protein in urine[101] and the use of the polymerase chain reaction to detect spirochetal DNA in host material[102]; neither has been perfected for clinical use as of this writing.

Several commonly performed laboratory tests may be abnormal early in the illness. The erythrocyte sedimentation rate is often modestly increased. The level of serum aspartate aminotransferase (AST or SGOT) is often mildly elevated during ECM, particularly in patients with prominent systemic symptoms. The level of this enzyme generally returns to normal within several weeks of disease onset. Total serum IgM levels are also often increased early in disease; a persistent increase of IgM, which correlates with specific IgM antibody levels, is a predictor of an increased risk of subsequent disease manifestations.[2,7] Patients may be mildly anemic early in the illness and occasionally have elevated leukocyte counts with a left shift in the differential. A few patients have had transient microscopic hematuria, sometimes with mild proteinuria (dipstick), but renal function has been normal. Throughout the illness, serum complement levels are generally normal or elevated. Tests for rheumatoid factor and antinuclear antibodies are usually normal.

Differential Diagnosis

Erythema chronicum migrans is the unique herald lesion of Lyme disease. When present in its classic form, there is little else that might be confused with it. Many patients, however, are unaware of having had ECM; in others, the lesion may be atypical in appearance. When multiple skin lesions are present, the appearance may suggest erythema multiforme, but blistering, mucosal lesions and involvement of the palms and soles (all features of erythema multiforme) are not features of Lyme disease. Rarely, patients with early Lyme disease have a malar rash suggesting systemic lupus erythematosus. Generalized urticaria has occurred and may suggest the diagnosis of the prodromal phase of hepatitis B infection or serum sickness. Finally, evanescent blotches and circles may resemble erythema marginatum, a cutaneous manifestation of acute rheumatic fever, but evanescent lesions in Lyme disease do not expand.

Lyme disease may be difficult to diagnose definitively early if flulike symptoms predominate, especially when ECM is absent or inapparent at the time of presentation. Severe headache and stiff neck may resemble aseptic meningitis, and, indeed, cerebrospinal fluid findings in Lyme meningitis are identical to those of viral meningitis. One helpful feature in this regard may be that the headache of Lyme disease tends to be intermittent. When generalized lymphadenopathy is present, particularly with splenomegaly, various diseases are suggested, including infectious mononucleosis and lymphoproliferative disorders.

In later stages, Lyme disease may mimic other systemic inflammatory disorders. Like rheumatic fever, Lyme disease may be associated with sore throat (rarely a prominent feature) followed by migratory polyarthritis and carditis, but without evidence of valvular involvement or of a preceding streptococcal infection. With isolated joint involvement, the clinical picture can be indistinguishable from reactive arthritis. Isolated peripheral seventh cranial neuropathy may mimic idiopathic Bell's palsy, but Lyme disease is one of the few causes (along with Guillain-Barré syndrome and sarcoidosis) of bilateral Bell's palsy. Late neurologic involvement may suggest multiple sclerosis (transverse myelitis), Guillain-Barré syndrome (symmetric peripheral neuropathy), or brain tumor. In children, the attacks of arthritis, although generally shorter, may be identical to those seen in the oligoarticular form of juvenile rheumatoid arthritis, but without iridocyclitis.

Treatment

The major goal of therapy in Lyme disease is to eradicate the causative organism. Like other spirochetal diseases, Lyme disease is most responsive to antibiotics early in its course. Treatment regimens have evolved over time, based on both controlled clinical data and on clinical experience. Because of the difficulty in proving that bacteria have been eradicated and the common persistence of some symptoms long after treatment, the end point of antibiotic therapy is not always clear. The treatment regimens presented here represent guidelines that will no doubt be refined in time (Table 2).

Early Lyme Disease

If patients are treated early with oral antibiotics, ECM typically resolves promptly, and major later sequelae (myocarditis, meningoencephalitis, or recurrent arthritis) usually do not occur.[17] Prompt treatment is therefore important, even though such patients may be susceptible to reinfection.[103] For adults, antibiotic choices in order of preference include oral doxycycline, 100 mg twice a day; amoxicillin, 250 to 500 mg three times a day; or erythromycin, 250 mg four times a day; each for 10 to 20 days depending on the rapidity of clinical response. Failures are more common with erythromycin use than with the other two agents. In children younger than 9 years, amoxicillin, 30 mg per kg per day (not less than 1 gram or more than 2 grams per day), is given in divided doses for the same period or, in cases of penicillin allergy, erythromycin, 30 mg per kg per day, in divided doses for 10 to 20 days.

About 10% of patients with early Lyme disease experience a Jarisch-Herxheimer-like reaction (higher tempera-

TABLE 2.—*Antibiotic Regimens for Various Manifestations of Lyme Disease**

Lyme Disease	*Drug*	*Daily Dosage*	*Length of Course, days*
Early disease	Doxycycline	100 mg 2x/d	10-21
	Amoxicillin	500 mg 3x/d	10-21
	Erythromycin	250 mg 4x/d	10-21
Neurologic manifestations			
Facial palsy alone	Doxycycline	100 mg 2x/d	10-21
	Amoxicillin	500 mg 3x/d	10-21
	Erythromycin	250 mg 4x/d	10-21
Other (such as meningitis)	Penicillin G	20 million units IV	14-21
	Ceftriaxone	2 grams IV	14-21
Lyme carditis			
Mild	Doxycycline	100 mg 2x/d	30
Moderate to severe	Penicillin G	20 million units IV	14-21
	Ceftriaxone	2 grams IV	14-21
Lyme arthritis	Doxycycline	100 mg 2x/d	30
	Amoxicillin and probenecid	500 mg of each 4x/d	30
	Penicillin G	20 million units IV	14
	Ceftriaxone	2 grams IV	14

IV = intravenous

*Current antibiotic regimens are based on both controlled clinical studies and clinical experience and will no doubt be refined in time. Antibiotic failures occur at all stages of disease, but, in general, the illness is most responsive to antibiotic therapy early in its course.

ture, redder rash, or greater pain) during the first 24 hours of antibiotic therapy.[17] Whichever drug is given, 30% to 50% of patients have brief (hours to days) recurrent episodes of headache, musculoskeletal pain, and fatigue that may continue for extended periods.[17] The cause of these symptoms is unclear; they may result from undegraded spirochetal antigen(s) rather than persistence of live spirochetes. It is clear, however, that the risk of delayed resolution is greatest in persons with disseminated manifestations of disease (multiple skin lesions, headache, fever, lymphadenopathy, or Bell's palsy) before the institution of antibiotic therapy.[17]

Later Lyme Disease

For Lyme meningitis, with or without other neurologic manifestations (cranial neuropathy or radiculoneuropathy), intravenous penicillin G, 20 million units a day in six divided doses for ten days, is effective therapy.[18] Headache and stiff neck usually begin to subside by the second day of therapy and disappear by seven to ten days; motor deficits and radicular pain frequently require seven to eight weeks for complete recovery but do not require longer antibiotic courses. For Bell's palsy alone, oral regimens may suffice, but these patients may be at higher risk of later sequelae than are persons with early disease without neurologic dissemination.

Although not studied systematically, carditis also responds rapidly (in days) to this regimen. The use of prednisone, 40 to 60 mg a day in divided doses, has, in the past, seemed to hasten resolution of high-grade heart block, but one should hesitate to institute glucocorticoid therapy during antibiotic administration as it may impede the eradication of infecting organisms.[5] For patients with allergy to penicillin, doxycycline, 100 mg twice a day, is reasonable but unevaluated. If second- or third-degree heart block is present, patients should be admitted to hospital for cardiac monitoring; temporary pacing is occasionally required for complete heart block.

In clinical practice, ceftriaxone (2 grams a day for 14 to 21 days) has largely replaced penicillin for the treatment of disseminated Lyme disease. Arguments in favor of this practice are a once-a-day administration schedule that is amenable to outpatient intravenous antibiotic programs and improved penetration of the cerebrospinal fluid in comparison with penicillin.[104,105] Penicillin and cefotaxime have been found equally effective for the treatment of acute neurologic Lyme disease (meningitis or radiculitus) in a group of patients studied in Germany.[106]

Late Lyme Disease

Lyme arthritis has been successfully treated with both oral and parenteral antibiotics, but failures occur with any regimen chosen. Unless central nervous system involvement coexists, first-line treatment with a month-long course of doxycycline, 100 mg two times a day, or amoxicillin plus probenecid, 500 mg each four times a day, is recommended. Either of these regimens has a 70% cure rate, although complete response can be delayed as long as three months or more following completion of therapy.[106] During treatment, the affected joint should be kept at rest and effusions drained by needle aspiration as for any infected joint. In a double-blind placebo-controlled trial, 7 of 20 patients given intramuscular benzathine penicillin, 2.4 million units a week for three weeks, were cured (mean follow-up 33 months) versus none of 20 control patients.[19] This regimen provides low serum levels of penicillin for about six weeks. High-dose intravenous penicillin G (above), which yields much higher serum levels over its ten-day course, cured 11 of 20 patients, including 2 in whom benzathine penicillin therapy had failed.[19] In one comparative trial, ceftriaxone (2 grams a day for 14 days) outperformed intravenous penicillin, but failures have occurred with both agents.[105,107] In patients in whom one course or more of antibiotics fail, arthroscopic synovectomy can result in a long-term response and perhaps cure.

Optimal therapy for the later neurologic complications of Lyme disease is also not yet clear. The frequency of subtle chronic encephalopathy and peripheral neuropathy is debated at present. These disorders, when suspected, should be carefully documented through neurologic, neuropsychological, and electrophysiologic testing before aggressive or prolonged antibiotic therapy is instituted. Although some current thinking favors longer periods of the highest tolerated oral doses of amoxicillin (with probenecid), doxycycline, or even intravenous antibiotics in difficult cases, there is no controlled experience with courses of antibiotics longer than one month for any manifestation of Lyme disease. The infiltrative lesions of ACA are usually cured by three weeks of oral phenoxymethyl penicillin, 2 to 3 grams a day in divided doses.[108]

Pregnancy

Because the spirochetes that cause relapsing fever and syphilis can cross the placenta, there has been concern regarding this possibility in Lyme disease. Maternal-fetal transmission of *B burgdorferi* resulting in either neonatal death or stillbirth has been reported in rare instances in which symptomatic early Lyme disease occurred early in pregnancy and was either untreated or inadequately treated.[50-51] In follow-up studies conducted by the Centers for Disease Control, maternal Lyme disease was not directly implicated as a cause of fetal malformations.[109] There have been no cases of

fetal infection occurring when currently recommended antibiotic regimens for Lyme disease have been used during pregnancy. A lower threshold for initiating therapy for suspected Lyme disease in pregnancy is understandable, but women acquiring the illness during pregnancy should be reassured that the vast majority of infants born to women in these circumstances have been entirely well.

Tick Bites

A final treatment issue regards the advisability of administering antibiotics prophylactically to persons sustaining ixodid tick bites in endemic areas. The single study completed to date has not supported this common practice.[110] Because nymphal ixodid ticks must, in general, feed for a day or more before transmitting spirochetes (at least in mice[111]), ticks removed before this time are unlikely to have transmitted *B burgdorferi* even if infected. Tick-bite sites should be observed for the development of ECM and patients cautioned regarding the common associated symptoms of early Lyme disease.

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Epitomes

Important Advances in Clinical Medicine

Otolaryngology/Head and Neck Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in otolaryngology/head and neck surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in otolaryngology/head and neck surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology/Head and Neck Surgery of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Intranasal Ethmoid Sinus Surgery, 1980 to 1990

In 1985 endoscopic intranasal ethmoid sinus surgery, a more precisely done ethmoidectomy targeting earlier paranasal sinus disease and leaving a more normal-looking nose, was introduced into the United States. The procedure usually includes a middle meatal widening or opening rather than the classic nasal antral or inferior meatal window. Improved teaching methods using video equipment and observer scopes have enabled an increasing number of physicians to treat the ethmoid sinuses without the trepidation that existed previously. An increased awareness of the anatomy of the ethmoid sinus relative to the other paranasal sinuses and the use of computed tomography have helped in this breakthrough. The potential for injury due to the ethmoid sinus's proximity to the eye and anterior cranial cavity persists, however.

With experience with endoscopic surgical procedures, it has become increasingly clear that limitations still exist regardless of how the procedure is done, whether with a headlight, endoscope, or an operating microscope.

Important advances have also been made by nonendoscopic sinus surgeons in treating lower respiratory tract disease, in particular the triad of aspirin, nasal polyposis, and asthma. A more aggressive or thorough or even destructive type of procedure has been advocated in dealing with such disorders. In 1980, 50 patients underwent extensive sphenoidethmoidectomy and nasal antral windows. Of 28 cortisone-dependent asthma patients, 26 had a sustained reduction or elimination of corticosteroid use, with half being steroid-free for a period ranging from six months to four years.

Improved results were obtained when a more radical sphenoidethmoidectomy procedure was used in combination with nasal polypectomies and nasal antral windows. When a less destructive, anatomically conservative procedure was adhered to, no more than a 25% resolution in lower respiratory tract problems occurred. In a more recent study, a better than 75% improvement occurred in asthmatic patients, especially cortisone-dependent ones, when a more aggressive procedure was used.

In a controlled study involving 25 patients with the aspirin, nasal polyposis, and asthma triad, 9 patients undergoing aggressive pansinus surgical treatment, including nasal polypectomies, sphenoidethmoidectomies, and Caldwell-Lucs, all showed a marked resolution of the underlying disease. In 16 patients who underwent limited or less aggressive procedures, including intranasal ethmoidectomy and polypectomy, 6 required surgical revision for disease control.

BERKELEY S. EICHEL, MD
Torrance, California

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Treatment of Vocal Cord Paralysis

Unilateral vocal cord paralysis is most commonly treated by the administration of polytef (Teflon) paste through direct or indirect laryngoscopy. The technique has been used for more than 40 years. It is relatively quick and inexpensive, although the vocal results achieved by the procedure have recently been questioned. Temporary injections of absorbable gelatin sponge (Gelfoam) paste and Zyplast collagen, lasting four to six weeks and three to six months, respectively, may be done in patients with acute paralysis who may recover. These techniques provide voice restoration during the recurrent laryngeal nerve's recovery period. In those patients in whom recovery does not occur, other more permanent techniques may be used.

In 1974 a different approach was introduced in which a small window is cut in the thyroid cartilage and the vocal cord moved medially by placing a polymeric silicone or other alloplastic "shim" or spacer. This approach eliminates the need for an injectable permanent material. Proponents of this technique cite its reversibility and, because patients are able to phonate during the procedure, the ability to "tune" the voice intraoperatively by adjusting the implant's placement. The vocal results achieved by experienced surgeons are reported to be comparable to those with polytef injection. Voice and speech scientists cite a better mucosal wave on videostroboscopy than that achieved with polytef injection.

Because the technique is reversible and does not affect the recurrent laryngeal nerve's ability to regenerate, it is feasible to do it immediately after recurrent laryngeal nerve injury, offering yet another option to those patients in whom vocal cord function may return.

Anastomosing the ansa hypoglossi (cervicalis) nerve to the recurrent laryngeal nerve offers a third alternative in the rehabilitation of unilateral paralysis. This procedure, although not capable of restoring cyclical vocal cord adduction and abduction, appears to restore vocal cord tone, hence improving the voice in a more physiologic manner than polytef injection or thyroplasty. Most otolaryngologists administer polytef, and some have learned the thyroplasty technique. Nerve transfer has been used in only a few centers in the United States. Until further data regarding thyroplasty and nerve transfer are available, the final decision regarding which procedure is used must be based on a laryngologist's experience.

ROGER CRUMLEY, MD
Irvine, California

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Phonatory Diagnosis and Phonosurgery

PHONATORY DIAGNOSIS involves the anatomic, vocal, and physiologic examination of the larynx. In any patient with vocal dysfunction, an anatomic evaluation is essential to rule out a potentially treatable malignant, inflammatory, or neurologic disorder. Since the time of Bozzini (1806) and Garcia (1854), the larynx has been visually examined by indirect mirror laryngoscopy. Rigid telescopes now provide the clearest, best illuminated views in awake patients. Flexible nasal fiberoptic laryngoscopy also provides excellent views even in uncooperative patients or those with difficult anatomy; gagging is virtually eliminated. Flexible or rigid endoscopic images may be recorded on video equipment for restudy and for patient education. Stroboscopic illumination calibrated nearly, but not exactly, to the fundamental frequencies produced by a patient's larynx gives a slow-motion view of the cycle of the vibrating vocal cords. This and ultrahigh-speed photography have delineated a vertically oriented mucosal wave that can be disrupted by the smallest mucosal alteration. A "clean" mucosal wave is required for optimal voice production.

A vocal examination of the larynx includes precise acoustic measures, such as airflow duration, frequency, range, intensity, and voice stability. The most important aspect of the vocal assessment remains subjective and is simply the "ear" of the voice professional and of the patient.

Physiologic tests of laryngeal function are less commonly used. Electromyography is useful for determining denervation versus reinnervation or fixation. The procedure may also be useful in the early diagnosis of degenerative neurologic disorders. In electroglottography, a potential difference occurs across the anterior neck. Current flows when the vocal cords are in contact, which provides an electrical correlate of vocal cord approximation. The vocal cords are supported by a relatively immobile cartilaginous framework; contraction is largely isometric and leads to tension. Because vocal-fold intramuscular pressure correlates with tension, monitoring the intramuscular pressure may provide diagnostic information in a variety of neuromuscular disorders.

Once the cause of the phonatory disorder is identified, proper treatment can be instituted. Malignant neoplasms and inflammatory disorders are treated as necessary. A laryngeal procedure may be done solely to change the voice. Administering polytef (Teflon) is the time-honored technique for moving the vocal cord medially, and it may be done under local or general anesthesia. It is not reversible and does not address vocal cord tension problems. When done skillfully, results may be superb, but some patients do not tolerate polytef well; granuloma formation and extrusion may occur. The laryngeal framework operation allows surgeons to alter the position and tension of the vocal cord without touching the cord itself. The vocal cord may be moved medially or laterally; it may be tensed, relaxed, or a combination thereof. By altering only the laryngeal framework, the mucosal wave is not disrupted. These procedures are done with the patient awake and vocalizing. This allows a fine tuning of the voice with simultaneous viewing of the glottis on a videoscreen. These procedures are adjustable and reversible. Reinnervating a paralyzed larynx is also occasionally an option. A traumatized nerve can be reapproximated with variable results. For recurrent laryngeal nerve paralysis, a nerve muscle pedicle transfer from the ansa cervicalis nerve can be used to help maintain vocal cord tone, position, and possibly appropriate motion with respiration.

In summary, with current diagnostic techniques, the specific deficit causing vocal dysfunction may be identified. Using the proper technique, the deficit often may be reversed and the voice improved.

ERIC F. PINCZOWER, MD
Los Angeles, California

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Skull Base Surgery

UNTIL RECENTLY, extensive tumors originating in the nose and paranasal sinuses, the orbit, the nasopharynx, and in the parapharyngeal space that extends to the bones of the undersurface of the anterior and middle cranial fossa were considered by head and neck surgeons to be inoperable and usually incurable. Tumors from the clivus, the meninges, and the skull base skeleton that extended into the deep recesses of the face were similarly considered to be unresectable by neurosurgeons. The combination of a head and neck surgeon, neurosurgeon, and, when needed for reconstruction, a plastic surgeon is now able to eradicate these tumors completely and to rehabilitate many of these patients. The team approach is paramount for a successful result. Nonsurgical disciplines such as neuroradiology and angiography in the preoperative evaluation; pathology and anesthesia intraoperatively; and radiotherapy, nursing, and prosthodontics postoperatively are integral for the overall successful care of these patients.

Previously established barriers to complete resection, such as anterior cranial floor invasion, extension to the orbital apex, sphenoid sinus involvement, cavernous sinus and internal carotid artery involvement, and intracranial extension, can all be handled in carefully selected patients.

For lesions involving the anterior cranial fossa, a transfacial incision with an approach through the maxillary and ethmoid sinuses is combined with a low anterior craniotomy. Total tumor excision can be accomplished even when dura and brain are involved. On occasion, an approach to the middle fossa through a subcranial route can achieve exposure of the cavernous sinus, eustachian tube, and internal carotid artery.

Middle fossa involvement is more difficult to manage and usually requires an infratemporal fossa and middle cranial fossa combined approach. Temporal lobe involvement and invasion of Meckel's cave, the cavernous sinus, and the petrous and cavernous carotid artery can all be safely managed through this approach.

The postoperative course may be stormy, and the availability of a dedicated or a neurosurgical intensive care unit with specially trained nurses is invaluable.

Three- to five-year tumor-free survival figures are being compiled by many centers doing skull base surgical procedures. Results are encouraging, especially in light of the hopeless prognosis otherwise facing these patients.

PAUL DONALD, MD
Sacramento, California

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Functional Endoscopic Sinus Surgery in Children

FUNCTIONAL ENDOSCOPIC SINUS SURGERY is an operative approach to the paranasal sinuses in which the objective is to reestablish adequate sinus ventilation and mucociliary clearance in patients with chronic sinus disease. Narrow mucosal-lined channels exist in the middle meatus where there is a high potential for mucosal layers to contact each other. The various ostia of the anterior ethmoid, frontal, and maxillary sinuses drain in proximity to this area. Because of mucosal hyperplasia and inflammation following an infection or allergy, these channels (and subsequently the ostia) may be blocked with resultant sinus obstruction. The effect on the sinuses may be either reversible (acute sinusitis) or irreversible (chronic sinusitis), depending on the source and time course of the original insult to the middle meatus-anterior ethmoid complex. This middle meatus-anterior ethmoid complex has been called the ostiomeatal unit or complex.

In the United States, endoscopic sinus surgical techniques have replaced open techniques in many instances. Many children treated with endoscopic sinus operations have considerable atopy, allergy, asthma, and primary and secondary immunodeficiencies. Other clinical groups include children with cystic fibrosis and immotile cilia or Kartagener's syndrome.

Children with chronic sinus disease, as confirmed by the history, physical examination, and repeated plain sinus films, may be treated with an endoscopic sinus operation. An adequate allergic and immunologic workup should be done before referral to an otolaryngologist-head and neck surgeon. It should be emphasized that an adequate trial of medical therapy is always completed before any consideration of operative intervention. The initial diagnostic evaluation always includes nasal endoscopy under topical anesthesia. This may be difficult, if not impossible, depending on the age and cooperation of the child. The middle meatus is carefully examined for evidence of chronic infection. Depending on the history and extent of the disease, medical therapy is often continued or altered and the patient reevaluated at a later date. Children who continue to have persistent disease after adequate medical therapy undergo direct coronal computed tomographic evaluation of the ostiomeatal complex and paranasal sinuses.

If the computed tomographic scan shows mucosal disease involving the ostiomeatal complex and ethmoid and maxillary sinuses, an endoscopic sinus operation may be considered. In children, the procedure requires a general anesthetic and is done on an outpatient basis under endoscopic visualization. The key to the operation is opening the ostiomeatal complex, but it may include a complete ethmoidectomy if the disease is extensive. Middle meatal antrostomies are created to open the natural ostia of the maxillary sinuses. Our experience thus far has been with 38 children who have undergone an endoscopic sinus operation. Of this number, most have been children with chronic sinus disease who are otherwise normal. As of this writing, an overall success rate of about 85% has been obtained in this group in terms of resolving symptoms of chronic sinus disease. Children with chronic sinus disease and concomitant hematologic disorders who are also receiving chemotherapeutic agents have responded similarly. Children who are atopic, with significant allergy and asthma, have responded well initially, including notable abatement of their asthma. Approximately half have had a relapse of their sinus and pulmonary symptoms six months to a year following the first procedure. Further follow-up and experience are necessary.

DENNIS M CROCKETT, MD
Los Angeles, California

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Cochlear Implants in Children

THE COCHLEAR IMPLANT is a medical device, part of which is placed surgically, that uses electrical stimulation to provide hearing. In recent years, the device has become an accepted method for providing auditory stimulation to the profoundly deaf. Two devices, the 3M/House single-channel cochlear implant and the Nucleus multichannel cochlear implant, have been formally approved by the United States Food and Drug Administration (FDA) for commercial marketing to deaf adults. More than 600 children ages 2 through 17 years have been implanted with either a single- or a multielectrode device.

In September 1988, the FDA's Ear, Nose, and Throat Advisory Panel voted to recommend marketing approval of

the 3M/House implant for children, mirroring the widespread professional acceptance of such devices in children. The 3M device is no longer available, but the Nucleus multichannel cochlear implant received FDA marketing approval for use in children in June 1990.

Extensive auditory, speech, educational, and psychological testing is done before and after implantation for children. Results show that cochlear implants provide auditory detection over much of the speech signal. Compared with before implantation, there is considerable improvement in auditory discrimination and speech production skills. Limited open-set word and sentence recognition is possible for at least some children, perhaps as many as 30%. Complications with the device have been minimal but include inappropriate placement of the electrode array, postauricular flap infection, facial paresis, transient dizziness or pain, and partial device extrusion. About 1% of patients in the Nucleus clinical trials had unresolved complications.

Selection criteria include bilateral profound sensorineural deafness, a lack of substantial benefit from hearing aids, psychological suitability, and medical suitability. The primary criterion for selection is confirmation of profound sensorineural hearing loss, usually with an average unaided threshold for the speech frequencies of poorer than 110 dB or an aided speech detection threshold of poorer than about 53 dB. Patients who are candidates show poorer performance on selected auditory discrimination tasks while using appropriately fit hearing aids than those using an implant. Families and, if possible, candidates should be well motivated and possess appropriate expectations. Medical contraindications include deafness caused by lesions of the acoustic nerve or central auditory pathway, active middle ear infections, cochlear ossification that prevents electrode insertion, an absence of cochlear development, and tympanic membrane perforation.

The cochlear implant can provide sound to deaf adults and children unable to benefit from hearing aids. The complex assessment, rehabilitation, and counseling should be done by centers with the multidisciplinary staff necessary to provide effective care for patients with this special auditory prosthesis.

WILLIAM F. HOUSE, MD
Newport Beach, California

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Anticytoplasmic Autoantibody Test for Wegener's Granulomatosis

WEGENER'S GRANULOMATOSIS is a systemic disease characterized by necrotizing laryngeal granulomas with vasculitis of the upper and lower respiratory tract, systemic vasculitis, and focal necrotizing glomerulitis. The disease can be limited or generalized. When there are nasal, pulmonary, and renal findings, a clinical diagnosis and histologic confirmation by nasal or kidney biopsy are relatively simple.

In Wegener's disease with limited and localized findings, such as isolated laryngeal subglottic involvement, diagnosis may be difficult. Not every nasal or laryngeal biopsy specimen will demonstrate characteristic histologic findings. The finding of a nonspecific inflammatory infiltrate is more likely.

The anticytoplasmic autoantibody test has been shown to have high specificity for Wegener's granulomatosis. The test was also useful to monitor reactivation and remissions of the disease. The absence of the autoantibody does not rule out Wegener's disease. The test is useful in diagnosing the disease in patients in whom histologic confirmation is not always possible—such as those with isolated subglottic stenosis. The test is done with a standard immunofluorescence technique. The cytopreparation is considered positive for anticytoplasmic autoantibody if the characteristic focal, centrally accentuated, fine granular cytoplasmic staining pattern is present in most neutrophils. Experience with pattern recognition and strict adherence to the methodologic protocol are essential for obtaining reproducible and reliable results.

LAWRENCE W. DE SANTO, MD
Scottsdale, Arizona

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Gadolinium Magnetic Resonance Imaging in Bell's Palsy

IT HAS BEEN DISCOVERED that the facial nerve in Bell's palsy has a characteristic appearance on gadolinium-enhanced magnetic resonance imaging (Gd-MRI) scans. Despite this important advance in imaging technology, the clinical presentation remains the mainstay of diagnosis. The diagnosis of Bell's palsy in the past has been one of exclusion, arrived at when a rapid onset of facial weakness is unaccompanied by signs or symptoms suggestive of disease involving the central nervous system, temporal bone, or parotid gland. More than 80 causes have been identified that result in facial paralysis. Many patients with serious underlying diseases affecting the facial nerve, such as tumors and infections, have been inappropriately given the diagnosis of Bell's palsy. Such a misdiagnosis may delay needed therapy and diminish the probability of eventual nerve recovery. When a facial palsy has atypical features, the diagnosis of Bell's palsy should be questioned, and a Gd-MRI scan of the nerve obtained. The most common reason for doing a Gd-MRI scan is weakness that persists for a longer period than would be expected in an uncomplicated Bell's palsy. When paralysis persists beyond two months, the diagnosis of idiopathic paralysis should be questioned. Other atypical features include slowly progressive palsy, facial palsy accompanied by spasm, recurrent palsy, unusual degrees of pain, and the presence of multiple cranial neuropathies or other neurologic symptoms.

On Gd-MRI scans, the facial nerve in Bell's palsy appears bright because of gadolinium uptake in the inflamed segment. This is usually most pronounced in the region of the geniculate ganglion at the lateral end of the internal auditory canal, but more diffuse enhancement of the intratemporal portion may be seen. This enhancement typically persists for several months and may not resolve entirely, even after paral-

ysis has abated. The Gd-MRI appearance tends to confirm the theory that Bell's palsy results from viral mononeuritis. Swelling of the nerve within the tight confines of the fallopian canal in the temporal bone results in ischemia and eventual neural dysfunction. The diameter of the nerve is the key difference between Bell's palsy and tumors involving the nerve. In Bell's palsy, the nerve is bright but not swollen or otherwise distorted, whereas in tumors, the nerve is typically both bright and focally enlarged. Gadolinium-MRI scans of patients with facial palsy should include the entire course of the facial nerve, from its exit from the brain stem to its terminal branches on the face.

In the recent past, clinicians managing a patient with atypical or persistent facial palsy faced a dilemma. If imaging studies were normal, the cause could be either atypical Bell's palsy or a subtle anatomic lesion beyond the resolving capacity of computed tomography or an unenhanced MRI study. The ability to make a positive diagnosis of Bell's palsy with Gd-MRI is reassuring to patients and clinicians. Indeed, many patients with Bell's palsy fear they have had a stroke, and an MRI scan may occasionally be warranted to allay those fears. A possible use for Gd-MRI in Bell's palsy stems from the preliminary observation that the degree of gadolinium enhancement correlates with the prognosis for the recovery of facial function. When intense gadolinium uptake involves a long segment of the nerve, a prolonged clinical course and incomplete recovery appear more probable.

MICHAEL J. LANSER, MD
ROBERT K. JACKLER, MD
San Francisco, California

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Laser Therapy for Early Cancer of the Vocal Cords

"EARLY," SUPERFICIAL squamous cell cancer, limited to mucous membrane of the membranous portion of the vocal cord, can be treated with an 80% to 90% chance of cure with irradiation or surgical therapy. Surgical resection in the past was by cup forceps removal (stripping) of the mucosa of the membranous vocal cord. It is now done more precisely with a dry field using the laser through microdirect laryngoscopy.

For laser (or cup forceps) stripping to be successful, the cancer should not invade more than 1 to 2 mm below the basement membrane of the mucosa, and the best results, of course, are obtained when it is a squamous cell carcinoma in situ.

Normal vocal cord mobility is an indication that there is no invasion into Reinke's space just below the mucosa, much less into the thyroarytenoid muscle. This is confirmed with a suction tube tip by palpation of the involved vocal cord through direct laryngoscopy. The abnormal mucosa is then excised with a 1-mm normal mucosal margin and a thin layer of normal connective tissue under the lesion. The lesion needs to stop at least 1 mm from the anterior commissure, its lateral edge should be visible on the floor of the ventricle (thus not go up into the false vocal cord), it should not extend onto the body and preferably not onto the vocal process of the arytenoid, and it should not go more than 3 to 4 mm below the free edge of the vocal cord. The margins should be clear and sharp.

The disadvantage of laser treatment is that irradiation achieves an equal five-year survival rate of about 90% and is equally effective when there is some invasion or spread slightly onto the arytenoid or onto the anterior opposite vocal cord or when margins are not sharply delineated. Although radiation therapy takes six weeks and can leave dryness in the throat, its main advantage is that it achieves a better voice on average than vocal cord stripping, even when the latter is done by an experienced laser surgeon through microdirect laryngoscopy. In summary, irradiation is advised as the primary therapy for T_1 and $T_2N_0M_0$ vocal cord squamous cell carcinoma. In carefully selected patients, however, especially after irradiation has failed, and if the lesion still meets (and originally met) the described criteria, laser resection of the lesion with a small margin around and beneath it may be a good alternative to vertical hemilaryngectomy or total laryngectomy.

HERBERT H. DEDO, MD
San Francisco, California

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Autoimmune or Immune-mediated Causes of Deafness

CERTAIN FORMS OF rapidly progressive sensorineural hearing loss have an autoimmune or immune-mediated basis. Patients with these forms commonly have bilateral ear involvement that begins as fluctuating hearing loss but becomes progressive and often profound. There is an accompanying disequilibrium or outright ataxia if the vestibular system is also affected. About 20% to 30% have associated, definable manifestations of systemic autoimmune disease, such as systemic lupus erythematosus, polyarteritis nodosa, or ulcerative colitis. Diagnosis is difficult because no certain means exists to identify this disorder. The use of lymphocyte transformation against inner ear antigens has led to different results. Recent studies using a Western blot immunoassay against crude inner ear antigen have shown some diagnostic promise; of 54 patients with rapidly progressive hearing loss, 19 were positive on Western blot, but only 1 of the 14 (7%) normal persons showed a similar band.

Other means of evaluating this disorder include a sedimentation rate, the antinuclear antibody test, and C1q binding and Raji cell assays. These nonorgan-specific tests help identify a generalized autoimmune state in a patient.

Treatment consists of a trial of high-dose steroids—prednisone, 60 mg daily for three to four weeks. Improved hearing will often be evident after three weeks. Maintenance on alternate-day therapy should be attempted with as low a dose as possible, as long as hearing is maintained. Some investigators recommend giving cyclophosphamide—2 to 5 mg per kg of body weight a day—in patients who do not respond to steroids and who are not of childbearing age, as the drug has potential oncogenic risks.

There is a need for a prospective, multicenter study to document the most effective diagnostic and treatment regimens for this disorder. Early results indicate, however, that patients can achieve substantial hearing improvement or stabilization with immunosuppressive therapy.

JEFFREY P. HARRIS, MD, PhD
San Diego, California

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Transoral Approach to Mandibular Angle Fractures

FRACTURES OF THE ANGLE are among the most common seen in mandibular fractures. Intermaxillary fixation with or without interosseous wires has been a major component of the treatment of angle fractures, but the fixation wires must stay in place for six weeks.

Mandibular plating has recently gained in popularity, as the fixation wires can be removed immediately. This technique works well on the body of the mandible, but angle fractures can be troublesome. The disadvantages of using plates at the angle include the need for a large skin incision and the possibility of damage to the facial nerve. An alternative is to plate the mandible through an intraoral incision just behind the third molar. Strict attention must be paid to the effect of the forces that the muscles of mastication apply to the ends of a fracture. A mandibular miniplate is used to direct the forces of mastication to compress the fractured ends together. This does not provide completely rigid internal fixation allowing the immediate removal of the intermaxillary fixation, as placement of a larger plate would, but it does avoid a large external incision.

The recommended period of intermaxillary fixation is two weeks, as opposed to six for other techniques. At that point, the patient is reevaluated and may be placed in elastic band fixation for one more week, or the fixation may be removed if the fracture is stable and the reduction is good.

The advantages of this technique are that there is no external incision, these smaller mandibular miniplates are easier to contour properly and should not be visible through the skin, the fixation requires a shorter time, and the ease of surgical approach and placement leads to a shorter operative time.

MARK N. SEGAL, MD
Albuquerque, New Mexico

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Alerts, Notices, and Case Reports

Alteration of the Natural History of *Pneumocystis carinii* Infection in Patients With Acquired Immunodeficiency Syndrome Receiving Aerosolized Pentamidine

DAVID M. KATES, MD
TERENCE G. SPARLING, MD, FRCP(C)
NAZMA JETHA, MD, FRCP(C)
DAVID R. BURDGE, MD, FRCP(C)
Vancouver, British Columbia

Pneumocystis carinii is the most common opportunistic pulmonary infection in patients with the acquired immunodeficiency syndrome (AIDS), but extrapulmonary and disseminated infection remains rare. We report the case of a severely immunocompromised man in whom disseminated *P carinii* infection developed while he was receiving secondary aerosolized pentamidine prophylaxis. Several factors, including profound immunocompromise and the use of nebulized pentamidine prophylaxis, likely contributed to the development of extrapulmonary pneumocystosis in this patient. We discuss the recent literature concerning disseminated *P carinii* infection[1-8] and comment on the probable pathogenesis and natural history of this infection.

Report of a Case

The patient, a 36-year-old man with AIDS, was admitted to hospital in July 1989 for the treatment of *P carinii* pneumonitis. Seropositivity to the human immunodeficiency virus (HIV) had been documented in March 1988, when an initial episode of *P carinii* pneumonitis was successfully treated with intravenous pentamidine. A regimen of zidovudine (azidothymidine) was started, and in July 1988 he began a program of aerosolized pentamidine prophylaxis using a Fisoneb nebulizer. Five loading doses of 60 mg of pentamidine isethionate were administered over ten days, and he was then maintained on 60 mg by nebulizer every two weeks, receiving a total of 34 treatments.

He was readmitted in July 1989 with cough, dyspnea, fever, night sweats, malaise, and weight loss. He was cachectic, febrile, and appeared chronically ill. Oral candidiasis was present, and his spleen tip was palpable 3 cm below the left costal margin. Diminished breath sounds and inspiratory crepitations were noted at the bases of both lungs.

The leukocyte count was 1.2×10^9 per liter with 0.7 polymorphonuclear leukocytes and 0.2 lymphocytes. The hemoglobin was 107 grams per liter (10.7 grams per dl) and the platelet count 54×10^9 per liter. Lymphocyte studies showed 0.0×10^9 per liter OKT4 (helper) cells. An arterial blood gas analysis showed a pH of 7.46, a P_{CO_2} of 39 mm of mercury, and a P_{O_2} of 79 mm of mercury with a bicarbonate of 28 mmol per liter and an O_2 saturation of 0.96. Serum levels were as follows: total protein, 56 grams per liter; albumin, 25 grams per liter; γ-glutamyltransferase, 73 U per liter (normal, 12 to 53); aspartate aminotransferase, 158 U per liter (normal, 12 to 35); lactate dehydrogenase, 2,059 U per liter (normal, 297 to 537); and creatine kinase, 1,884 U per liter (normal, 60 to 330). Blood cultures were sterile. A lumbar puncture revealed a normal cell count, differential cell count, glucose and protein levels, and the cerebrospinal fluid was negative for cryptococcal antigen. Cerebrospinal fluid cultures for virus, fungi, and acid-fast bacilli were sterile. A VDRL was negative, and a serologic test for *Toxoplasma* species was negative. A bone marrow aspirate and biopsy were nondiagnostic. An initial abdominal ultrasound examination revealed the spleen to be 14 cm in size, but the results were otherwise normal.

A reticular interstitial bilateral infiltrate was seen on chest x-ray films. Bronchoalveolar lavage and brushings revealed numerous cysts of *P carinii*. Parenteral pentamidine therapy failed, but the patient did respond to parenteral administration of the combination of trimethoprim and sulfamethoxazole with complete clearing on his chest x-ray film and a resolution of pulmonary symptoms. At this point, he was noted to have hepatomegaly, and a repeat ultrasound study (one month after the initial study) showed multiple tiny hyperechoic lesions throughout the liver parenchyma. The spleen measured 15 cm in size, and there were multiple hyperechoic lesions through the spleen, kidneys, and pancreas as well.

A liver biopsy specimen revealed multiple caseating granulomata (Figure 1). Stains for acid-fast bacilli and fungi were negative, and cultures were sterile. Cysts of *P carinii* were demonstrated (Figure 2).

Pancytopenia developed with the administration of trimethoprim-sulfamethoxazole. Oral dapsone and trimethoprim therapy was started, and, despite the findings on liver biopsy, the patient improved clinically, gained weight, and

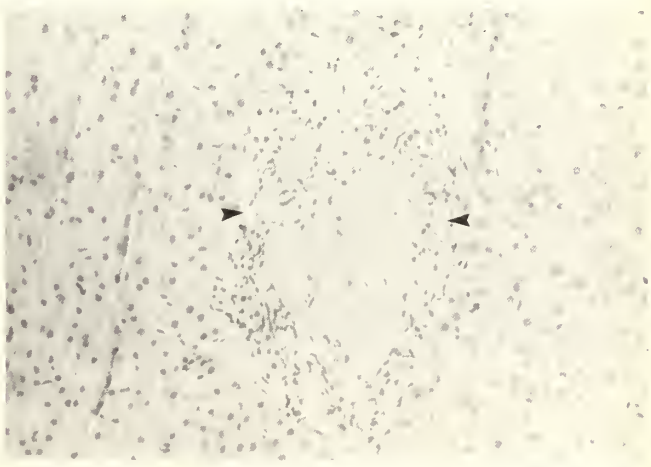

Figure 1.—A liver biopsy specimen shows a loosely formed granuloma with central necrosis **(between two arrowheads)** (hematoxylin and eosin, original magnification × 200).

(Kates DM, Sparling TG, Jetha N, Burdge DR: Alteration of the natural history of *Pneumocystis carinii* infection in patients with acquired immunodeficiency syndrome receiving aerosolized pentamidine. West J Med 1991 Jun; 154:721-723)

From the Department of Medicine (Dr Kates); the Division of Hematology, Department of Medicine (Dr Sparling); the Department of Anatomical Pathology (Dr Jetha); and the Division of Infectious Diseases, Department of Medicine (Dr Burdge), University Hospital—Shaughnessy Site, University of British Columbia, Vancouver.

Reprint requests to David R. Burdge, MD, FRCP(C), Division of Infectious Diseases, University of British Columbia, University Hospital—Shaughnessy Site, G611, Jean Matheson Pavilion, 4500 Oak St, Vancouver, BC, V6H 3N1.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

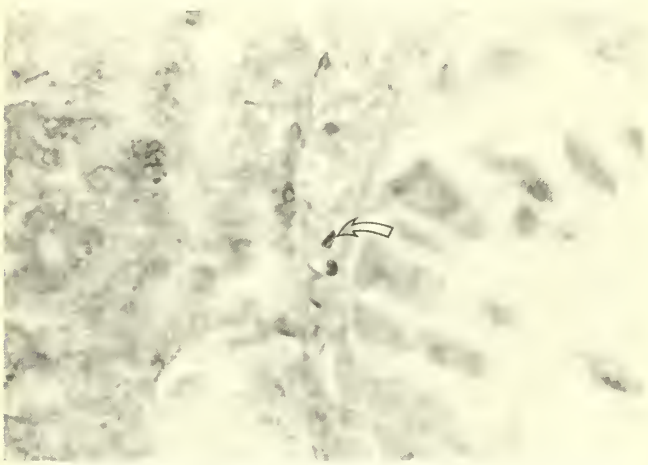

Figure 2.—A *Pneumocystis carinii* cyst **(open arrow)** is shown at the periphery of the necrotic zone seen in Figure 1 (Grocott stain, original magnification × 400).

was discharged home. Because of gastrointestinal intolerance, trimethoprim was discontinued and he has subsequently been maintained on a regimen of oral dapsone, 100 mg daily, and clindamycin, 450 mg four times a day. Follow-up ultrasound studies of the abdomen have shown no appreciable change in the multiple hyperechoic lesions in the liver, spleen, and kidneys. His course has been complicated by gradual weight loss and cytomegalovirus chorioretinitis, but he remains alive with a reasonable quality of life ten months after the hospital discharge.

Discussion

Extrapulmonary and disseminated infection with *Pneumocystis carinii* remains rare, and several large autopsy series failed to find the organism outside of the lungs.[9,10] When reported, extrapulmonary pneumocystosis has usually occurred in patients with overwhelming pulmonary infection.[9] Two of us (T.G.S. and D.R.B.) and colleagues have recently reported the occurrence of disseminated *P carinii* infection in a severely compromised AIDS patient with no evidence of pulmonary involvement, and Hardy and co-workers have reported a similar case.[2] In both of these cases, the patients were receiving secondary prophylactic aerosolized pentamidine therapy. These two cases, and the further case reported herein, join a series of recent reports of extrapulmonary *P carinii* infection, all of which have occurred in patients receiving prophylactic aerosolized pentamidine.[3-8,11]

Shelhammer and associates have shown that even with successful treatment as judged clinically and radiographically, *P carinii* cysts are not eradicated from the lungs.[12] It is therefore not surprising that recurrences of *P carinii* pneumonia are common in the absence of some form of prophylactic therapy. Various prophylactic measures have decreased the recurrence rate of the pneumonitis, including the use of oral zidovudine trimethoprim-sulfamethoxazole, pyrimethamine, sulfadoxine, dapsone, and parenteral pentamidine.[2] Aerosolized pentamidine has also been shown to be effective prophylactically against recurrent *P carinii* pneumonia and has recently been recommended for routine use for this indication by both the Centers for Disease Control[13] and Health and Welfare Canada.[14] Minimal systemic toxicity and documented efficacy in the setting of secondary prophylaxis have also resulted in the recent recommendation that primary prophylaxis with aerosolized pentamidine be initiated in all HIV-infected patients with low OKT4 (helper) cell counts.[13]

Pharmacokinetic studies by Conte and Golden,[15] Montgomery and colleagues,[16] and Salamone and Cunha[17] have shown that the concentration of pentamidine in bronchoalveolar lavage fluid following aerosolized administration is high—10 to 75 times greater than drug levels achieved with intravenous infusion—following inhalation therapy. The half-life of the drug in bronchial fluid is prolonged; detectable levels have been observed in one patient as long as 115 days following the completion of a two-week course of therapy. Systemic absorption is minimal, and accumulation in plasma has not been observed. This pharmacokinetic finding appears to support the hypothesis that aerosolized pentamidine suppresses pulmonary disease but might allow for the dissemination of the organism.[1]

It is noteworthy that in both cases of disseminated pneumocystosis that we have reported, patients have been severely immunocompromised, as reflected by OKT4 (helper) cell counts of 0.0×10^9 per liter (present case) and 0.017×10^9 per liter.[1] It may be that aerosolized pentamidine is not the sole factor resulting in dissemination and that profound immunocompromise must also be present. Unfortunately, the majority of reported cases of extrapulmonary *P carinii* infection do not include documentation of CD4+ cell counts. It will be relevant to observe whether dissemination also occurs in less compromised patients receiving aerosolized pentamidine, such as those receiving primary pneumocystis prophylaxis. Further study is required before it can be concluded that the severely immunocompromised state is a necessary cofactor for the development of disseminated *P carinii* infection.

The natural history of extrapulmonary *P carinii* infection is not yet clear. In both of our patients, the infection has been indolent, and they have remained well for several months following diagnosis. Optimal modalities of therapy are also unknown, and it remains to be seen whether prolonged systemic therapy alters the natural history of the infection.

In all severely immunocompromised patients who are receiving aerosolized pentamidine therapy, the diagnosis of disseminated pneumocystosis must be considered when systemic symptoms or hepatosplenomegaly or lymphadenopathy develop. Liver and lymph node biopsies are helpful in establishing the diagnosis. We anticipate that disseminated pneumocystosis will be seen more frequently with the increasing use of aerosolized pentamidine prophylaxis. Innovative prophylactic regimens that include systemic prophylaxis (perhaps in combination with aerosolized pentamidine) deserve further consideration and study.

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Tonic Spasms in Multiple Sclerosis

Anatomic Basis and Treatment

LAWRENCE S. HONIG, MD, PhD
PHILIP H. WASSERSTEIN, MD
Stanford, California

BRUCE T. ADORNATO, MD
Palo Alto, California

TONIC SPASMS are among several paroxysmal symptoms of multiple sclerosis. Although first described decades ago, they are frequently misdiagnosed, and they have not been well localized. We present the case of a 31-year-old man with the sole complaint of stereotyped, left-sided, painful tonic spasms primarily affecting the arm, with less involvement of leg and face. Hyperventilation reliably precipitated the spasms.

Report of a Case

The patient, a 31-year-old right-handed man, was seen because for six weeks he had had intermittent "muscle spasms" involving the left side of his body. They typically began in the left shoulder and progressed distally to the arm, hand, and fingers. There was simultaneous involvement of his left hip and leg. The feeling of muscle tension was accompanied by uncontrollable shaking and spasmodic movements of the affected parts, with the fingers "going every which way automatically." In addition, a pins-and-needles tingling sensation that was unpleasant and painful developed in the left limbs. The left side of the face was involuntarily drawn up, and he spoke with effort. There was no headache, nausea, vomiting, tinnitus, diplopia, or visual, mental, or sphincteric disturbances preceding or during the attacks, nor were any residual sensory or motor deficits noted.

When these attacks had first started, the patient went to an emergency department. No episodes were witnessed there, and the results of an examination were normal. A diagnosis of "muscle spasm: no neurologic disease" was made, and he was instructed to consult a neurologist should the episodes continue. The episodes were initially only a few seconds in duration and occurred once to three times per day, but over a month's time they increased in severity and frequency, lasting 15 to 60 seconds and occurring as often as three times per hour. While originally benign, they became troublesome to the patient, interfering with his driving and at one point causing him to drop a beverage glass.

His medical history included a period of several months of diplopia at age 12, requiring "visual training classes," but resolving without medical or surgical therapy. He had sustained minor injuries in vehicular accidents, but his only operation was a tonsillectomy at age 7. His habits included two-packs-per-day tobacco smoking and moderate daily alcohol use. No medications or street drugs were being taken.

On general physical examination, no abnormalities were noted. His mental state was notable for anxiety, inappro-

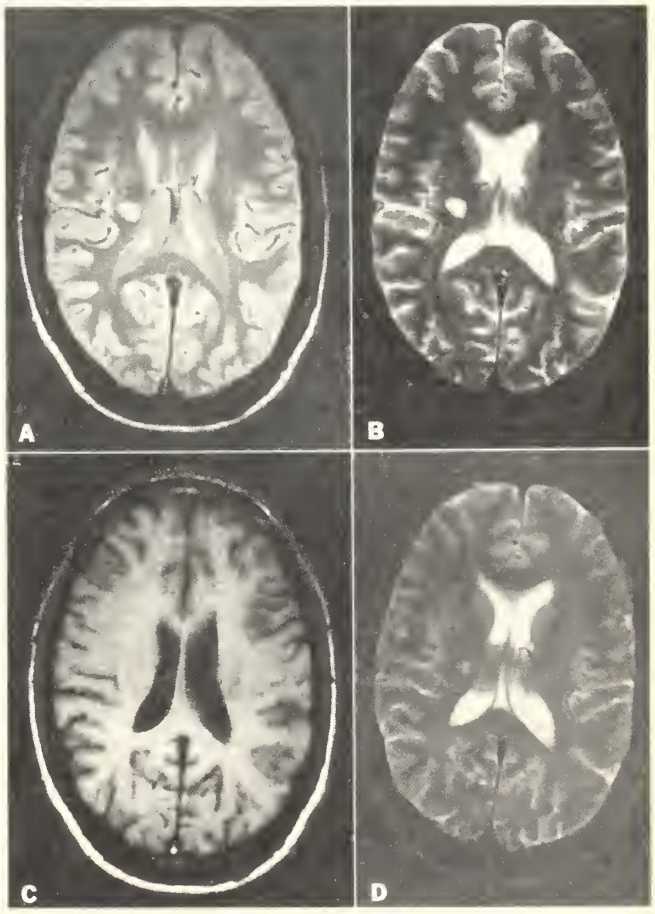

Figure 1.—Brain magnetic resonance imaging: Spin-echo sequences include a proton-weighted first-echo (TR = 2,000, TE = 20 milliseconds) image (**A**) that shows a right internal capsule abnormality with greatly increased signal intensity on a T2-weighted second-echo (TR = 2,000, TE = 80 milliseconds) image (**B**) but no signal abnormality on a T1-weighted (TR = 800, TE = 20 milliseconds) image (**C**). Two months later, the lesion size and signal intensity are decreased, as shown in a T2-weighted image (**D**).

(Honig LS, Wasserstein PH, Adornato BT: Tonic spasms in multiple sclerosis—Anatomic basis and treatment. West J Med 1991 Jun; 154:723-726)

From the Department of Neurology and Neurological Sciences, Stanford University Medical Center, Stanford, California.

Reprint requests to Lawrence S. Honig, MD, Department of Neurology and Neurological Sciences (H-3160), Stanford University Medical Center, Stanford, CA 94305-5235.

ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
Ig = immunoglobulin
MRI = magnetic resonance imaging

priate affect, social disinhibition, and increased psychomotor activity. A cranial nerve evaluation, including fundi, elicited entirely normal findings, as did the motor system examination, with normal bulk, tone, strength, gait, and coordination throughout. Sensory testing revealed mild hypesthesia to light touch, pinprick, and vibration on the left hemibody with respect to the midline; proprioception and stereognosis were normal. Muscle stretch reflexes were present and symmetric. No pathologic reflexes were found.

Laboratory studies included normal serum electrolytes, general chemistry panels, urinalysis findings, and hematologic studies, with a sedimentation rate of 2 mm per hour. Serum was negative for fluorescent treponemal antibody absorption, VDRL, fluorescent antinuclear antibody, and rheumatoid factor; serum angiotensin-converting enzyme level, protein electrophoresis, chest roentgenogram, and electrocardiogram were normal. A lumbar puncture yielded clear, colorless cerebrospinal fluid (CSF) with an opening pressure of 150 mm of water. Cell counts were erythrocytes, 10×10^6 per liter, and leukocytes, 13×10^6 per liter, with 0.98 lymphocytes and 0.02 monocytes; the glucose level was 3.4 mmol per liter (61 mg per dl), protein 440 mg per liter, and VDRL negative. A CSF protein analysis by agarose electrophoresis showed a normal albumin level of 168 mg per liter (normal, 130 to 240) and CSF:serum albumin ratio of 0.004 (normal, <0.009), reflecting an intact blood-brain barrier. Elevated levels, however, of immunoglobulin (Ig) G of 72 mg per liter (normal, <55), fraction IgG of 0.164 (normal, <0.105), IgG index of 1.87 (normal, <0.7), and a calculated IgG synthesis rate of 24 mg per day (normal, <3) all suggested central nervous system (intrathecal) immunoglobulin synthesis. The CSF also showed oligoclonal banding, with 2 bands present in the gamma region, without counterparts in the serum.

Hyperventilation for two minutes produced characteristic attacks of left arm flexion and dystonic hand posturing with pain and tremulousness lasting about a minute. The left side of the face also contorted, the head turned to the left, and the left leg tensed.

The electroencephalogram was normal; neither epileptiform activity nor changes in background were seen during or after tonic attacks documented on simultaneous video monitoring. Visual and brain-stem auditory evoked potentials were within normal limits: P100 latencies were 99 milliseconds bilaterally. Somatosensory evoked potentials showed poorly formed P40 cortical responses on stimulation of the left posterior tibial nerve, but they were otherwise normal.

Treatment with carbamazepine (Tegretol), 400 mg per day in divided doses, resulted in the prompt abatement of both spontaneous and hyperventilation-induced spasms. After three months, a trial discontinuation of carbamazepine therapy was pursued and there was no recurrence of attacks off medication. Eight months later, a dense right facial palsy of a lower motor neuron type developed, accompanied by decreased hearing on the right side. This facial paralysis resolved little over the subsequent nine months despite two courses of oral steroid therapy.

At the initial presentation, brain x-ray computed tomography showed a small region of lucency in the posterior limb of the right internal capsule that failed to enhance with intravenous contrast dye. Magnetic resonance imaging (MRI) showed this area, measuring about 2 cm in diameter, as abnormal signal centered in the posterior limb of the right internal capsule extending into adjacent thalamus. The lesion displayed increased signal on the proton-weighted (TR = 2,000, TE = 20 milliseconds) spin-echo image (Figure 1-A), and more intense signal on the T2-weighted (TR = 2,000, TE = 80 milliseconds) image (Figure 1-B), but on a T1-weighted (TR = 800, TE = 20 milliseconds) pulse sequence (Figure 1-C), it possessed normal signal and was not identifiable. Follow-up imaging two months later, when the patient was asymptomatic, showed decreased lesion size and signal intensity on proton (not shown) and T2-weighted (Figure 1-D) images. A third MRI study (no figure) done eight months after the onset of facial palsy, when the patient was without spasms off medical therapy, revealed some further resolution of the capsular abnormality, without the appearance of new lesions.

Discussion

This 31-year-old man had the subacute development of stereotyped, painful tonic spasms involving the left upper extremity and the left side of his face. He had a history of a childhood period of diplopia and a long-standing behavioral disorder. The spasms could be brought on reliably by hyperventilation. When carbamazepine therapy was instituted, both spontaneous and induced attacks disappeared.

The differential diagnosis of stereotyped unilateral body movements without alteration of consciousness includes epileptic seizures, psychogenic attacks, carpopedal spasm (tetany), paroxysmal kinesogenic choreoathetosis, and paroxysmal dystonic choreoathetosis, in addition to the tonic spasms of demyelinating disease. Aside from the fact that this patient's clinical attacks were classic for tonic spasms, none of the other disorders are associated with abnormalities of cerebral white matter. Simple partial epileptic seizures with motor manifestations often show abnormality on ictal scalp electroencephalography. Also, compared with tonic spasms, partial seizures tend to be less frequent, less readily provoked by hyperventilation, and less easily controlled by low doses of carbamazepine. Psychogenic attacks are always a consideration in spells for which objective confirmation is absent, but supportive criteria important for such a diagnosis include nonconformance of the attacks with known disorders, nonphysiologic variability between individual attacks, and some motivational explanation for the occurrence of psychogenic events. Carpopedal spasm (tetany) occurs with hypocalcemia or severe metabolic alkalosis; it is usually painless, bilateral, and longer lasting than a tonic spasm. Paroxysmal kinesogenic choreoathetosis is a rare condition featuring attacks of abnormal motor activity that are brief (seconds to minutes in duration), frequent (as many as 100 per day), and anticonvulsant-responsive. The attacks, however, are commonly induced by sudden movements, tend to be more complex than simple tonic postures, and usually begin at a younger age; also, there is often a family history of such a disorder. Paroxysmal dystonic choreoathetosis is another rare familial disorder. Attacks generally begin in early childhood, last as long as hours at a time, and rarely occur more often than three times a day. The attacks experienced by this patient were

most consistent with the tonic spasms (described later) associated with demyelinating disease.

Multiple sclerosis was ultimately diagnosed in this patient based on the presence of central nervous system lesions separated in time and location, with supportive laboratory (CSF) evidence. While the tonic spasms, the lesion seen by MRI, and the somatosensory potential abnormalities all fit a diagnosis of a single central lesion, additional history included the previous clinical episode of diplopia and a subsequent attack of a dense and unremitting facial palsy. Although this latter lesion was of lower motor neuron type, such facial palsy may occur in multiple sclerosis, presumably from involvement of the intramedullary portion of the seventh cranial nerve root. The MRI signal of the right basal ganglion lesion (Figure 1) was characteristic, although not specific, for a demyelination plaque, as was its subsequent resolution without specific therapy. Cerebrospinal fluid examination showed abnormalities consistent with multiple sclerosis, including mild lymphocytic pleocytosis, elevated central nervous system IgG synthesis, and the presence of oligoclonal IgG bands.

Paroxysmal attacks including dysarthria, ataxia, falling, and tonic spasms are features of multiple sclerosis that are not always recognized as such.[1-19] Tonic attacks are commonly unilateral, with consciousness preserved, and may occur, as in this patient, as the presenting symptom.[2-6] Their nomenclature has not been agreed on and has included tonic spasms,[7] tonic seizures,[2,3,8,10] paroxysmal dystonia,[6] tetanoid attacks,[2,4] and sensorimotor seizures.[10,11] We prefer the term tonic spasms, which is descriptive and distinguishes these white matter phenomena from cortical (epileptic) seizures of grey matter origin. The tonic motor manifestations characteristically are accompanied by paresthesias, are frequently painful,[9,12] last about 30 seconds (range 10 seconds to 3 minutes),[1-12] and may occur repetitively many times per day.[2-4] They are unaccompanied by alteration or loss of consciousness[1-19] or by electroencephalographic epileptiform activity.[2,3,7,9] Tonic spasms frequently show provocative susceptibility to hyperventilation.[2-4,12] Attacks tend to abate spontaneously over months, probably with evolutionary change of the causative demyelinative plaque. Symptomatic treatment with phenytoin has variably shown success[2,3,6,7] or failure,[6,9] but carbamazepine therapy has shown the greatest efficacy in suppressing tonic spasms.[6,7,9,11,14]

Localization within the neuraxis of tonic seizures has been obscure. Some authors have suggested a spinal origin,[9-11] although involvement of the face, as in our patient, argues for a more rostral focus. Others have proposed a brain-stem or subcortical location.[2,15] Pathologic correlations have been few.[7,9] Indeed, Joynt and Green reported that "the location or locations will probably never be satisfactorily fixed because of the diffuse changes found in the nervous system."[3] Nonetheless, the development of x-ray computed tomography provided two reports of imaged single lesions in patients with tonic spasms, albeit in the context of accompanying fixed motor deficits in the affected limbs: a patient with a multiple sclerosis plaque in the internal capsule[19] and another with a putaminal infarct.[20] Our report (previously published in abstract form[21]) is to our knowledge the first of a case in which MRI, a most sensitive technique, was used to show only a single, isolated, demyelinating lesion. This plaque anatomically appears to affect descending corticospinal pathways on the right, correlating with typical tonic seizures in the left (contralateral) body in an otherwise motorically intact person. The lesion involves the posterior limb of the internal capsule, which can account for the face, arm, and leg motor and sensory involvement. Although in this patient the lesion involving the descending corticospinal tract was capsular, presumably other lesions of the pyramidal tract in, for example, the cerebral peduncle or lateral columns of the cord, might result in the same motor symptoms. Although the spinothalamic tract runs in close proximity to the corticospinal tract, the divergent levels of their decussation would seem to demand a supracervical location in those patients in whom pain is ipsilateral to the spasm. Alternatively, ipsilateral pain might not be due to the same primary process involved in the motor activity but to the provoked muscular contraction itself. There have been some cases reported in which sensory symptoms are crossed, being contralateral to the tonic spasms,[9-11,15] and these attacks presumably originate in the spinal cord.

The pathophysiology of tonic seizures might involve spontaneous discharges, ectopic excitation, or ephaptic transmission ("cross-talk") among abnormal (demyelinated) neuronal axons. In some cases, proprioceptive or tactile stimuli have elicited attacks,[7,9,16] perhaps lending support to an ephaptic mechanism. Lhermitte's phenomenon, in which mechanical flexion of the spine causes a paroxysmal sensory abnormality putatively mediated by the dorsal columns, likely represents a fleeting, sensory example of the same excitative phenomenon.[16] Hyperventilation commonly provokes tonic attacks, possibly increasing electrical irritability through vasoconstriction, with relative ischemia and hypoxia[17]; hypocapnia, with accompanying alkalosis; or altered calcium availability from alkalosis.[2,18] Relevant to these mechanisms is the reported suppressive role of acetazolamide.[22] The therapeutic efficacy of the anticonvulsants phenytoin and, particularly, carbamazepine may be related to the abilities of these agents to inhibit repetitive electrical discharges through effects on sodium channel conduction.

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Withdrawal Effects of Metoclopramide

A. MICHAEL NOLL, PhD
Los Angeles, California

DREW PINSKY, MD
South Pasadena, California

METOCLOPRAMIDE HYDROCHLORIDE is a powerful antiemetic that, among other helpful effects on the gastrointestinal tract, also stimulates gastric emptying.[1,2]

We report the case of a woman who took metoclopramide for about six months and experienced subtle adverse reactions. The drug was withdrawn, and the adverse reactions expanded, worsened greatly, and oscillated daily between akinesian (rigid) and akathisian (restless) symptoms. More than a year after the metoclopramide therapy was discontinued, the patient still shows adverse effects of the drug.

Report of a Case

Background

The patient, a 41-year old woman, was diagnosed by endoscopy as suffering from an ulcer. She was placed on a regimen of sucralfate (Carafate), 4 grams per day (four times a day), and metoclopramide hydrochloride (Reglan) at an initial dosage of 20 mg per day (four times a day) by her gastroenterologist. Two months later, the metoclopramide dosage was increased to 40 mg per day (four times a day).

About a month after the metoclopramide therapy was started, the patient had a weak menses. The next menses on day 30 was "short and spotty" according to the patient and was then followed by the complete cessation of menses. At that time, this problem was thought to be the result of a possible postconcussion syndrome from a recent head trauma that had occurred a few weeks after the metoclopramide regimen was started. The patient had been using crutches as a result of a knee operation, fell on a flight of stairs, hit her head, and lost consciousness. In retrospect, the metoclopramide was the most likely cause of the amenorrhea because it is well known to elevate serum prolactin levels, which would then halt the menses. Furthermore, the patient appeared to be recovering from the concussion.

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Dr Noll is with the Annenberg School for Communication, University of Southern California, Los Angeles. Dr Pinsky is in private practice in South Pasadena, California

Reprint requests to A. Michael Noll, PhD, Annenberg School for Communication, University of Southern California, Los Angeles, CA 90089-0281.

Adverse Reaction

About five months after the initial use of the metoclopramide, a variety of subtle symptoms became apparent, in addition to the continuing amenorrhea. These symptoms were somewhat episodic and included trembling of the hands and legs, an inability to sit still, complaints of difficulty in thinking clearly, staring blankly with diminished blinking, a greatly reduced libido, sweaty palms, and a feeling of warmth. The patient complained of feeling anxious, and sustained resting tachycardia developed. Because metoclopramide causes nearly identical adverse reactions, withdrawal was initiated.

Withdrawal Syndrome

The metoclopramide was withdrawn with an immediate decrease to 10 mg per day followed ten days later by a complete withdrawal. Just before the initiation of the graduated withdrawal, the patient's serum prolactin level, measured in a blood specimen drawn in the morning, was 139 μg per liter (normal < 20).

During the ten-day withdrawal period, many of the previously noted adverse reactions worsened. In addition, the patient reported nausea, galactorrhea, and frequent urination of modest volumes. The patient's palms and soles were sweaty, and a rigidity appeared, particularly in the hands.

After the complete withdrawal of the metoclopramide, her symptoms worsened greatly and some new symptoms appeared, such as a crawling sensation on the arms (dysesthesia). The only improvement was in the serum prolactin level, which, measured two weeks after the withdrawal began, had returned to normal levels at 11 μg per liter. This confirmed our belief that the metoclopramide therapy, and not a postconcussion syndrome, was the cause of the amenorrhea.

After an initial period of about a week after complete withdrawal, a number of the withdrawal symptoms appeared to fall into two separate groups.* All symptoms disappeared during sleep. The patient frequently complained of difficulty concentrating and showed signs of depression.

The first group of symptoms consisted of features such as muscle tightness and rigidity, blank staring with a masklike facies, diminished blinking and dysphagia, jerky voluntary movement of the hands and arms, and a slight tremor at rest. Motor activity was severely decreased and bradykinetic, associated with a vocal apraxia. The patient complained of feeling warm, her palms were sweaty, and her skin temperature was elevated, but there was no fever. This group of symptoms will be called the rigid, or akinesian, set.

These features are all parkinsonian in nature and would appear to be associated with secondary parkinsonism.[3(p1422)] Noteworthy, however, is that such classic Parkinson's disease features as a "pill-rolling" movement of the fingers and "cogwheel" rigidity were absent.

The second group of symptoms consisted of such features as restlessness and agitation, foot tapping, pacing, involuntary choreiform movements with hemiballismus, and rocking and swaying of the upper body. This second group of symptoms is associated with motor restlessness (akathisia) and hence will be called the restless, or akathisian, set.[4] Many of these features are associated with tardive dyskine-

*The patient assisted in this report by keeping careful records of the details of her withdrawal symptoms.

sia, except that choreiform movements of the buccal, facial, and lingual muscles were absent.[5]

An episode involving the rigid, or akinesian, set of symptoms sometimes would terminate with an episode of sudden generalized myoclonus. At other times the termination would be gradual over a few minutes. On termination of the slow state, the patient would then feel cold and her palms would be dry.

The two sets of symptoms had a definite diurnal pattern. The restless set was most apparent about an hour after arising and would last about an hour, sometimes terminating in a rigidity lasting about ten minutes with abrupt myoclonus. The rigid set was most prominent in the late afternoon and would last about an hour. Evenings were usually free of most symptoms.

We categorized the withdrawal symptoms into two sets because that is the mutally exclusive way they occurred.

Recovery

The overall improvement in the condition of the patient was slow, though steady. Three or four good days relatively free of symptoms would be followed by three or four days in which the symptoms were worse.

Medications such as bromocriptine mesylate (Parlodel), levodopa (Larodopa), and benztropine mesylate (Cogentin) were considered but were not administered because of the patient's history of adverse reactions and of concern about worsening the situation.

The patient improved gradually over the first two months, but her ability to cope with the symptoms steadily declined, thereby leading to feelings of depression. At this time, it was thought that some intervention to the "cold-turkey" approach was warranted. Because we thought that she was oscillating between dopamine-depleted and dopamine-excess effects (explained in the Discussion section), a dampening agent was deemed desirable. Hence, a regimen of γ-aminobutyric acid (GABA), 750 mg per day, and levoglutamine, 500 mg per day, was initiated. Because some of the symptoms mimicked vitamin deficiencies, the patient was also given vitamin B_6, 50 mg per day, and magnesium, 250 mg per day, under the rationale that they might hasten her recovery. With the thought that it might help heal the damaged neuroreceptors, ergoloid mesylates (Hydergine) therapy was started at the same time at 3 mg per day. This regimen had an immediate and dramatic effect in greatly reducing the withdrawal symptoms, although it is not known which agent or combination of agents, or whether it was simply self-healing, caused the dramatic recovery that was observed. About eight weeks after the metoclopramide had been withdrawn, the patient's menses returned, although they were weak at first.

The vitamin B_6, GABA, levoglutamine, magnesium, and ergoloid therapy was stopped after two months because of a lack of further therapeutic response.

Seven months after the metoclopramide was withdrawn, the patient still showed signs, though subtle, of its adverse effects. She slept about ten hours per day, was easily irritated, and complained of low energy. Some parkinsonian features remained. The patient did return to work at this time and appeared to be pursuing a productive life.

As of this writing (14 months after the metoclopramide was withdrawn), the patient still has subtle symptoms, such as not being able to think clearly and memory difficulties.

The patient has a history of migraine headaches, but the frequency and intensity of the headaches seemed to increase while she was taking the metoclopramide. The elevated level of prolactin and associated amenorrhea might have resulted in the increase in migraine activity. Her migraines returned to their normal activity after withdrawal of the metoclopramide. Interestingly, bilateral ovarian cysts were diagnosed (and confirmed by ultrasonogram) about 11 months after the withdrawal of the metoclopramide. The patient had no antecedent history of ovarian cysts, no family history, and no previous menstrual abnormalities. It is interesting to consider metoclopramide's possible role in initiating this disorder.

Discussion

Metoclopramide is clearly a powerful and useful drug, but the long-term use of the medication led to adverse reactions, including serious effects that lasted long after the drug was withdrawn. We would suggest care in the use of metoclopramide for longer than two months.

Metoclopramide achieves its antiemetic properties through antagonism of D_2 dopamine receptors in the chemoreceptor trigger zone that controls emesis.[6] The observed reactions to the withdrawal of metoclopramide may be explained in terms of the actions of the drug on dopamine and dopaminergic receptors. Some adverse reactions to metoclopramide use occur early, and others develop more slowly. The antagonistic action of metoclopramide on dopamine receptors also tends to mask some of its own adverse reactions.

The fast-acting adverse reactions, according to research studies, are akathisia and elevated prolactin levels. A single dose (10 mg given intravenously) of metoclopramide caused akathisia within a half hour in about 25% of normal subjects that lasted for three to four hours.[7] A single dose (5 mg given intravenously) of metoclopramide caused an average 15-fold peak increase in prolactin levels above the basal level in 16 female control subjects.[8] This peak value had reduced to only half after about two hours from the initial administration of the metoclopramide.

The long-term and withdrawal reactions can be explained by different mechanisms. An increase in the density of dopamine receptors along with behavioral supersensitivity has been reported in rats as a result of the long-term administration of metoclopramide.[9] If we assume a similar result in humans, an increase in dopamine receptors would develop to compensate for the dopaminergic antagonist action of the drug. This greater density of receptors would be expected to result in an exaggerated response, or supersensitivity, to dopamine, but the antagonism of the metoclopramide would mask such effects. This insidious action makes it difficult to observe the development of adverse reactions until it is too late. By then, the damage to the density of dopaminergic receptors has been done, and presumably a fair amount of time is needed for the receptors to achieve a normal density and sensitivity to dopamine.

Assuming that this is what happened with the patient in this report, then once the drug was withdrawn, its antagonist effect would immediately cease, but the increased density of receptors would remain. This increased density of receptors would amplify the response to dopamine, and the patient would be supersensitive to even normal amounts and variations in dopamine.[10(p18)] A decrease in dopamine could result in parkinsonlike symptoms, and an increase in dopamine

could result in tardive akathisia-like symptoms. The system would be in oscillation between the states of both dopamine depletion and dopamine excess as it attempted to achieve equilibrium. As equilibrium was slowly achieved over time, possibly by a return to a density of dopaminergic receptors, the effects of the oscillations would lessen and the symptoms would gradually subside.

Given the suggested mechanism to explain the observed effects in this patient, we would expect adverse reactions and withdrawal effects of the long-term use of metoclopramide to occur frequently. The real surprise is the relative infrequency of reporting of such adverse effects. In fact, one study found only 479 reports of extrapyramidal reactions in nearly 16 million prescriptions of metoclopramide, and the overwhelming majority (95.0%) of the reactions were of a dystonic-dyskinetic nature.[6] The investigators, however, did suggest care in the use of the drug with girls and young women because they seemed especially susceptible to adverse reactions. Robinson concluded that reported extrapyramidal reactions were rare and were mostly of the dystonic variety.[11]

Adverse reactions have been documented with the long-term oral use of metoclopramide, however. Hyperprolactinemia and amenorrhea have been reported as being elicited by the long-term (nine months) use of metoclopramide.[12] Grimes and colleagues report parkinsonism, acute dystonic reactions, and tardive dyskinesia in 18 patients who had been treated long term with oral metoclopramide.[13] In seven of the patients, orobuccolingual dyskinetic movements developed when metoclopramide was withdrawn. The authors cautioned against the long-term use of the drug because of the potential development of irreversible tardive dyskinesia.[14,15]

Tardive dyskinesia was reported to develop in 11 elderly Swedish women treated on a long-term basis with metoclopramide.[16] An 84-year-old woman treated for eight months with metoclopramide had parkinsonian effects that disappeared in four to eight weeks after the drug was withdrawn, although tardive dyskinesia appeared on withdrawal and persisted six months later.[17] After eight months of treatment with metoclopramide, an 83-year old woman had tardive dyskinesia develop, which worsened when the drug was withdrawn.[18] Motor restlessness (tardive akathisia) and depression that worsened after the withdrawal of metoclopramide are reported in two patients, and the adverse reactions took 18 to 27 months to resolve completely.[19] One of the patients had a pronounced diurnal pattern, with symptoms worse in the mornings, along with an episodic pattern every few days.

The research conducted with rats that showed an increase in the density of dopamine receptors with a prolonged use of metoclopramide is important.[9] Extending this direction of research to determine the effects on receptor density after varying durations of the administration of metoclopramide, how quickly the receptor density returns to normal after withdrawal of the drug, and what actions could be taken to hasten this recovery would be enlightening.

More care needs to be exercised in the use of metoclopramide, particularly with extended use of the drug. We are concerned that many of the adverse effects are easily confused with psychiatric disease and hence might lead to incorrect diagnoses. The drug's method of action and adverse effects are similar to those of antipsychotic or neuroleptic drugs; we therefore wonder whether metoclopramide could be classified as an antipsychotic or neuroleptic drug to warn physicians of its possible harm to some patients.

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Artificial Urinary Sphincter Erosion in Cardiovascular Surgical Patients

A Cause for Concern

JAMES R. FISHMAN, MD
ANTHONY R. STONE, MB, FRCSE
Sacramento, California

URINARY INCONTINENCE is a significant clinical problem affecting about 10 million adult Americans.[1] Treatment options have evolved with a greater understanding of the underlying disorder to include behavioral, pharmacologic, and surgical measures. The number of patients having iatrogenic urinary incontinence is increasing with a wider use of endoscopic surgical treatment of the bladder outlet and radical surgical therapy for prostate cancer.[2] For these patients, a prosthetic device simulating sphincter activity has been available for the past 20 years with the use of sphincter pros-

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From the Department of Urology, University of California, Davis, School of Medicine, Sacramento.

Reprint requests to Department of Urology, University of California, Davis, School of Medicine, 4301 X St, Suite 2210, Sacramento, CA 95817.

theses.[3] The Scott artificial urinary sphincter (model AMS 800) represents the state-of-the-art active continence device[4] at this time.

Artificial urinary sphincter placement is suitable for selected patients.[5] The long-term success of the device depends on this careful selection and on limiting the incidence of postimplantation complications,[6] particularly infection and erosion of the occlusive cuff into the urethra.[7] Patients with implanted artificial urinary sphincters need to alert their other physicians to the presence of the device, particularly when transurethral instruments may be used or open abdominal or pelvic procedures contemplated that might jeopardize the sphincter's integrity. Physicians need to assume responsibility for managing the sphincter, whether directly or through urologic consultation, to avert the above-mentioned complications.

Patients

We recently evaluated two patients with artificial sphincter cuff erosions due to urethral catheterization through an activated sphincter following cardiovascular procedures. In both patients, this complication required the removal of the device and reimplantation following six to eight months of healing.

Discussion

The two cases mentioned in this report unfortunately occurred because of an improper understanding of the artificial urinary sphincter. A simple awareness of the artificial sphincter's presence is of paramount importance. The device comprises three components (Figure 1): an inflatable cuff that encircles and occludes the bladder neck or the bulbous urethra, a pressure-regulating reservoir that provides pressures of varying ranges, and a central pump that allows cuff decompression; a control assembly within the pump mechanism regulates fluid transfer within the device. This assembly is implanted in the labia of women and the scrotum of men. The pump is activated by squeezing, thus transferring fluid from the cuff to the balloon, allowing voiding or the passage of a catheter. In two to three minutes, the cuff is automatically refilled by the pressure exerted by the balloon. A deactivation device was introduced with the AMS 800 model that allows a sustained decompression of the cuff.[2] This allows the cuff to remain empty during the immediate postimplantation period and, more important, allows atraumatic urethral instrumentation and catheterization if required.

Complications from the placement of the artificial urinary sphincter include urinary retention, cuff erosion, infection, and recurrent incontinence.[6] Cuff erosions can cause perineal pain, a bloody urethral discharge, hematuria, irritative voiding symptoms, or recurrent urinary incontinence. Cystoscopy and retrograde urethrography are used for diagnostic examinations. Erosions after the placement of an artificial urinary sphincter usually occur within three to four months and generally are caused by poor surgical technique, improper cuff sizing and placement, and the incorrect selection of a pressure reservoir. Before the delayed cuff activation after implantation was available, erosion occurred more frequently.

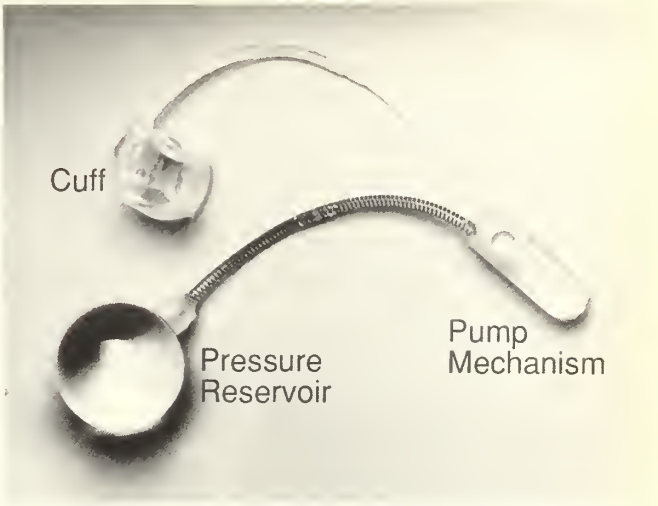

Figure 1.—The function of the AMS Sphincter 800 urinary prosthesis is described in this report (photograph courtesy of American Medical Systems, Inc, Minnetonka, Minnesota).

If a catheter is passed through an occlusive cuff, not only will the urethra be traumatized, but sustained compression of the urethra between the cuff and the catheter will cause ischemic damage, precipitating erosion. Large erosions require removal of the device, repair of the injury, and prolonged suprapubic catheter drainage. Smaller defects can be managed by urethral catheter drainage after removing the device. It is generally agreed that the reimplantation of another artificial urinary sphincter should be postponed for three to six months, with good results reported in selected patients.[7]

Clearly, with the increasing number of these devices implanted in elderly patients, physicians must be alerted to their presence. We counsel our patients carefully about this and also encourage them to wear a Medic Alert bracelet. Other physicians treating these patients must become acquainted with the device's function or consult with a urologist who understands it. These simple measures will prevent serious complications that require prolonged hospital stays and several additional surgical procedures before resolving.

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Commentary

Volunteering in West Africa

FRED WURLITZER, MD, *Burlingame, California*

A medical student or resident taking an elective or a physician thinking of volunteering might not know what to expect in a lesser-developed country. When deciding to work abroad, consideration should be given to licensing, immunizations, documentation, insurance, climate, political situation, and facilities.[1] Because firsthand accounts of medical practice in the Third World are few,[2-6] I will describe my experience volunteering in West Africa and suggest some priorities for improving medical care.

In late 1989 and on a separate trip in 1990, I spent six weeks as a visiting surgeon at the Kamakwie Wesleyan Mission Hospital in rural northwestern Sierra Leone. In 1989 I spent two weeks at the Vanga Baptist Mission Hospital, about 320 km (200 mi) southeast of Kinshasa, the capital of Zaire. During this eight-week period, I did 82 major and minor surgical procedures (Table 1) and saw many tropical diseases and obstetric problems.

The Kamakwie Hospital has 68 beds and the Vanga Hospital more than 200. Both facilities are so-called bush hospitals because they are located in rural, extremely undeveloped communities with populations of less than 10,000. Road access to the nearest metropolitan center is difficult, and resources are limited. These "medical centers," however, draw upon hundreds of thousands of people, many walking from more than 320 km away. Both centers routinely accept fourth-year American medical students taking electives.

These hospitals try to be independent of outside financial support other than for expatriate staff. They usually operate profitably, despite fees (Table 2) that are a fraction of those in the United States. Profitability is possible because labor costs are low. The average West African nurse makes about $10 (US) a month. Other medical personnel make less. Short-term medical volunteers usually pay for their room and board (about $15 a day) and transportation and receive no pay for their services.

In West Africa, physicians will encounter such threatening diseases as the acquired immunodeficiency syndrome (AIDS), malaria, and hepatitis. Most of the long-term personnel I met had had malaria at one time or another, and a week after returning home from my first visit, I developed it.

The common language in Zaire and in much of West Africa is French; in Nigeria, Ghana, and Liberia, it is English; and in Sierra Leone, it is Krio—a variant of English. "Word turners" or translators are available when patients speak dialects. Many West African hospitals are located where French is spoken and require that their physicians speak French.

A typical day began at 5:45 AM when the church bell tolled. After a cold shower—because there was no running hot water—we prepared for work. Each day ended about 10:00 PM when the power was cut off to conserve fuel for the electric generator. The hospitals saved many thousands of dollars a year this way, but we could not depend on electrically powered devices. Mechanical ventilators, suction apparatus, electrocardiographs, and other electrical equipment were not always available.

Seasonal variations in climate were small. Despite the long, hot, and humid days of work, we felt rested. Our diet was high in starch and low in protein. Mostly it was inexpensive imports, such as noodles and rice, combined with local lamb or chicken. We lacked telephones, newspapers, and television. Nearby towns had no restaurants or entertainment nor, for that matter, even electricity or running water. Our entertainment was one another and our work. Life seemed simpler, less stressful.

In a worldwide survey conducted by the American College of Surgeons,[7] the West African states and Tanzania had the lowest number of surgeons per 100,000 people. A shortage of physicians in all specialties exists in West Africa, compounded by an extreme maldistribution of surgeons to the urban centers.[8] Missionary physicians, who are typically family practitioners working in rural hospitals, carry the brunt of this surgical personnel maldistribution. Often the missionary physicians cannot cope with their operating caseload because it is too large, and multispecialty coverage is not nearby. A visiting surgical specialist, therefore, ordinarily has an opportunity to do a large number of surgical procedures in a short time. Even on brief visits, a surgeon or a family practitioner with surgical training can be of real service to staff and patients waiting for help. A sufficient number of visiting physicians is not available regularly.

My medical experiences in Africa were different from my work at home because of the variety and scope of surgical procedures I faced. I saw neurosurgical cases, orthopedic problems of unusual severity because of patient neglect, gynecologic and obstetric problems, and other major medical and surgical problems I seldom encountered in the United States (Table 1).

We saw so many hernias and hydroceles in Sierra Leone that a technician did these procedures to take a burden off the medical staff. Onchocerciasis was such a frequent cause of these problems that we often did skin biopsies to rule out this disease. Many hernias and hydroceles were of monstrous proportions requiring scrotal resections.

One patient, a man about 20 who had fallen from a palm tree some four months before, crawled and limped into Vanga

(Wurlitzer F: Volunteering in West Africa. West J Med 1991 Jun; 154:730-732)

Dr Wurlitzer is retired from private practice in Burlingame, California, and now works abroad from time to time.
Reprint requests to Fred Wurlitzer, MD, PO Box 2069, Burlingame, CA 94011.

from more than 320 km away with a complete break and nonunion of the right femur. I assisted a staff physician interested in orthopedics in doing open reduction using external pins. Many patients sought medical care months after compound fractures with osteomyelitis that required debridement and drainage of the bone. These patients often could not travel immediately to our centers after their injuries because of poor road networks.

Vesicovaginal fistulas were numerous because of unsupervised deliveries caused either by difficulties traveling or lack of education. These fistulas often became challenging surgical problems.

TABLE 1.—*Major and Minor Surgical Procedures Done by Author in an 8-Week Period in West Africa*

Procedure	*No.*
Head and Neck	
Caldwell-Luc	1
Cleft lip repairs	2
Deltoid-upper back flap (Bakamjian type) reconstruction of the posterior neck	1
Partial maxillectomy	1
Radical neck dissection	1
Neck exploration	1
Submaxillary gland resection	1
Thyroidectomy for goiter	3
Tonsillectomy	1
Tracheostomy	2
General Surgery	
Aneurysmectomy (false aneurysm of femoral artery)	1
Cholecystojejunostomy for biliary obstruction	2
Colon resection for inflammatory mass	1
Closure of perforated ulcer	1
Cystostomy	1
Exploratory laparotomy	4
Gastroenterostomy for obstructing gastric cancer	2
Radical groin dissection	1
Herniorrhaphy	
Ventral	1
Inguinal	3
Hydrocelectomy	
Simple	6
With scrotal resection	2
Mastectomy	
Simple	1
Modified radical	1
Orchidopexy	1
Orchiectomy	
Simple, for cancer of the prostate	1
With scrotal resections	3
Skin graft for tropical ulcer	2
Squamous cell carcinoma of the skin resection*	2
Gynecologic	
Cone biopsy of the cervix	1
Cesarean section	5
Destructive extraction of a fetus	1
Dilation and curettage	4
Hysterectomy	
Abdominal	2
Vaginal, for procidentia	2
Salpingo-oophorectomy	
Ectopic pregnancy	2
Ovarian tumors	2
Tuboplasty for infertility	1
Vaginal reconstruction (McIndoe)	1
Vesicovaginal fistula repair	
Simple	2
With vaginal flap	1
Miscellaneous	
Meningomyelocele repair	1
Incision and drainage	
For osteomyelitis	3
For tropical myositis	2
For rectal abscess	1
Syndactyly repair bilaterally	1

*Both resections were carried out in albinos.

During my eight weeks of service, I did not see any patients diagnosed with appendicitis, cholelithiasis, colon cancer, or lung cancer. One patient presented with a perforated gallbladder due to an inflammatory mass of unknown cause that obstructed the common bile duct. She required a cholecystojejunostomy, as did another patient who had a Courvoisier's gallbladder due to a stomach cancer. Two other patients required gastroenterostomies because of obstructing gastric carcinoma. This mix of operations was dissimilar to that reported from another West African bush hospital.[9]

Although visiting specialists will follow their interests and training, visiting general surgeons should be prepared to face a variety of surgical problems. Medical specialists also will be challenged by diverse problems.

Operating conditions were often uncomfortable. In Kamakwie, the operating room had air conditioning, but it was still so warm that a fan was needed to stay cool. In Vanga, because there was no air conditioning, we placed a fan as close to us as possible to avoid excessive sweating. Staying cool in the operating room became a challenge. Double gloving or wearing a rubber apron to lessen the chance of human immunodeficiency virus (HIV) transmission was usually impractical because of the heat.

At Kamakwie the operating surgeon administered anesthesia. We gave spinals for nearly all abdominal cases unless a patient was in shock. Otherwise, we gave short-acting ketamine hydrochloride without intubation. No nurses had training with inhalation anesthesia. At Vanga, where trained national nurses gave ether anesthesia with endotracheal intubation, we could do head and neck procedures more safely and easily.

Because of the need for economy, we used sutures conservatively by making instrument ties. Hand ties wasted materials, so we avoided them. We tried to get as many as 12 knots out of one suture strand—these were the "missionary ties."

The operating rooms did not run as smoothly as back home. We used resterilized needles, bandages, and scalpel blades repeatedly. Equipment and supplies were lacking or malfunctioned. Often we improvised or accepted materials that were not our first choice.

We guessed at postoperative electrolyte replacement therapy because blood chemistry measurements were not available. The laboratories did not do culture and sensitivities, so

TABLE 2.—*Fee Schedule for Common Operations at Komakwie Wesleyan Hospital, Sierra Leone*

Procedure		*Approximate Cost, in US $*
Hernia	Repair, single	8.00
	Double	10.00
Hydrocele	Repair, single	8.00
	Double	10.00
Scrotal resection	Additional	4.30
	Elective	5.00
Dilation and curettage	Elective	4.75
	Emergency	5.50
Laparotomy	Emergency	7.33
	Ectopic	8.00
	Hysterectomy	13.33
Prostatectomy		16.66
Vesicovaginal fistula repair		10.00
Tuboplasty		20.00

antibiotic therapy was also guesswork. Blood was typed but not crossmatched or checked for HIV. Outdated x-ray equipment limited examinations essentially to only the chest and long bones. We resorted to "tropical ultrasounds"—quick exploratory laparotomies—to make diagnoses.

Because one purpose of mission work is to help spread Christianity, physicians volunteering at a mission hospital must expect some religious exposure. Protestant chapel services were held every morning and prayers said before every operation in both centers.

My medical experiences broadened. Like other visiting physicians, I saw disease processes that are unusual in North America.[10] Two patients, a child and a man, presented with spinal cord paralysis from tuberculosis (Pott's disease). Hepatomegaly or splenomegaly was present in almost every patient. Splenomegaly meant malaria, and hepatomegaly usually meant schistosomiasis, not alcoholic cirrhosis.

In Zaire, the staff had diagnosed 22 new cases of AIDS on average each month for the preceding half year. One physician had seen about 1,000 cases in a five-year period in this isolated area. In contrast, in rural northwestern Sierra Leone, AIDS had not yet become common.

We could differentiate the patients with tuberculosis from those with AIDS only by testing. Many AIDS patients had tuberculosis or symptoms that mimicked other diseases. Limited resources prevented our treating patients who had AIDS and tuberculosis together.

Infectious diseases, many preventable by immunizations, abounded. I saw more than a dozen children die of meningitis, complications of measles, anthrax, and tetanus. Many adults with typhoid died. Polio crippled children. In addition to the problems caused by onchocerciasis, neglected orthopedic injuries, and complications of childbirth, a major obstacle to improved medical care in West Africa was the lack of sufficient preventive medicine, public education, and good transportation.

Data on prevention were not readily available or were kept haphazardly at both centers. Our efforts to immunize were minimal and consisted entirely of occasional efforts to vaccinate children in outlying villages. The first priority for offering better medical care in West Africa should be to send teams into villages specifically to provide vaccinations and information about sanitation. Because ultimately adequate health care systems must become independent of expatriate skills, training health teams is a corollary priority.

Although intervention by a visiting physician may not make much difference overall in the medical care in West Africa unless the problems of vaccinations and preventive care are solved, American physicians, medical students, or residents taking such an elective can enjoy the challenge of short-term volunteer work where so many medical problems occur that differ from those seen in developed nations. Some surgical training is important, but there are still many opportunities for medical personnel without surgical skills to improve medical care in lesser-developed regions.

Volunteers can contribute much and learn more. If physicians are interested in foreign service in West Africa or other lesser-developed areas, they should consult the article, "Directory Lists Overseas Service Opportunities for Physician Volunteers."[1]

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Editorials

The Fabric Is Sound but the Edges Are Fraying

It was a bad week. Rumor had it that the Centers for Disease Control might recommend mandatory human immunodeficiency virus (HIV) antibody testing for health care workers with patient care responsibilities. Reports surfaced about companies establishing unwritten rules to relieve HIV antibody-positive workers of their duties. And I was asked by an Occupational Safety and Health Administration official to discuss a new blood-borne pathogen regulation that would list discarded "female sanitary napkins" as biohazardous medical waste material. Was anxiety getting an upper hand? Were feelings overwhelming facts?

Observations and data are the bases of science. Science and compassion are the bases of medicine. Since 1980, 30,000-40,000 papers on HIV have appeared in English in medical journals. Since July 1990, this journal has published 17 papers, editorials, and letters on the subject. Topics ranged from basic science to diagnosis, treatment, ethics, and effects on public health, attitudes, and the profession. Yet another paper appears in this issue.[1] Data are certainly available. How can we use them to counter forces that lead to panic and chaos?

- We must read. We need to read more than headlines, recalling that the purpose of headlines is to attract, to sell, not to educate.
- We must remember the dictum we learned in pharmacology courses: One should not be the first, nor the last, to get on the bandwagon. Prescribing practices should not be swayed by the first paper about a drug, since additional information must be collected before safety and efficacy can be assured. On the other hand, one should learn about recent developments and modify the armamentarium when indicated. The same caveat holds true as we develop policies about HIV transmission and disease. One example out of millions of incidents is cause for interest and study but not for sweeping change.
- We must provide a steady supply of data-based information to our patients and the media, for we know that "fear of AIDS [is] inversely correlated with knowledge."[2]

Physicians have been a source of strength during past plagues, wars, and other disasters. Our fair-mindedness, our well-informed actions, our integrity help society stay tightly knit. Our steadiness, our direction, and our guidance help bind families and communities. Physicians' willingness to stay the course, to learn, to speak about HIV is crucial as nightmarish situations and proposals threaten to tear society apart. It isn't easy to insist upon more research when we are pressed for immediate but intemperate action in response to fear. Indeed, it takes courage to rely upon facts rather than emotions. Bertolt Brecht's play, *Galileo,* follows the great scientist's life as it was affected by his heliocentric theory of the solar system. Galileo recanted his theory when he appeared before the Inquisition. In Brecht's recounting, Galileo regrets abandoning his position, regrets caving in to coercion: "The practice of science would seem to call for valor . . . . As a scientist I had an almost unique opportunity . . . . Had one man put up a fight, it could have had wide repercussions. I have come to believe that I was never in real danger . . . I have betrayed my profession."[3] Just as observations, data, and compassion are necessary for good medicine, courage is also necessary as we work to reknit the ravelling sleeve HIV has presented to us.

LINDA HAWES CLEVER, MD

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The Molecular Genetics of Colorectal Carcinoma—Knowledge for Knowledge's Sake?

The molecular genetics of colorectal carcinoma are among the best understood of any common human cancer. Progress in this area has been aided by the nature of the disease. Colorectal carcinoma is frequent in the United States population: It is the second most common cause of cancer deaths, resulting in about 60,000 deaths yearly. Approximately 110,000 new cases of colonic carcinoma and 45,000 new cases of rectal carcinoma occur each year.[1] As a consequence, neoplasms for study are readily available. Second, the usual precursor lesion of colorectal carcinoma, the colorectal adenoma, is accessible at various stages in its development in specimens from surgical resection and colonoscopic polypectomy. This availability is in stark contrast to most human cancers in which the precursor cannot be obtained and studied easily. In addition, inheritance plays an important role in colorectal carcinoma. Two autosomal dominant syndromes are recognized. One, the adenomatous polyposis syndrome, predisposes to malignancy by producing hundreds to thousands of colorectal adenomas, with carcinoma occurring mainly in the left colon. The other syndrome, the hereditary nonpolyposis colorectal cancer syndrome, produces few adenomas (hence "nonpolyposis"), with carcinoma occurring mainly in the right and transverse colon.

Knudson's hypothesis that the same genes are involved in the genesis of sporadic and inherited forms of a tumor[2] suggests that these syndromes will provide important clues, and such has been the case. The APC [adenomatous polyposis coli] locus on the long arm of chromosome 5[3] and the MCC [mutated in colorectal carcinoma] gene in the same region[4] are altered frequently in "sporadic" colorectal cancer. Less well-defined inheritance of colorectal carcinoma is also evident. Pedigree studies of large families have suggested that the ability to form colorectal adenomas is inherited as an autosomal dominant characteristic.[5] Furthermore, the occurrence of colorectal cancer in first-degree relatives (parents, siblings, and offspring) of patients with the disease is about three to four times that of the general population.[6] Finally, environmental, particularly dietary, factors are well known to have a key role in the genesis of colorectal cancer, especially carcinomas of the left colon.[7] "Sporadic" carcinomas of the right and left colon have different molecular genetic alterations, with deletion of the p53 gene on the short arm of chromosome 17 a nearly universal finding in left colonic carcinomas but less common in right colonic carcinomas.[8] Thus, the groundwork for understanding the interaction of

environment and heredity is laid in colorectal carcinoma to a greater extent than in most other human cancers.

In this issue of the journal, Dennis Ahnen, MD, reviews the current state of knowledge of the genetics of colorectal cancer. He points out the complexity of the situation, with involvement of both dominant-acting oncogenes (*ras, myc, src*[9]) and suppressor genes that undergo inactivation or loss (DCC,[10] p53, APC/MCC, and probably loci on the short arm of chromosome 1[11] and the long arm of chromosome 22[12]). In addition, allelotyping of colorectal cancers reveals allelic deletions throughout the genome of some tumors,[13] raising the possibility of additional suppressor genes. As a further complicating feature, the phenotypic effects of altered suppressor genes can be produced by various mechanisms. In some suppressor genes, both alleles undergo inactivation, usually by mutation and deletion, eliminating all normal gene product. In other suppressor genes, however, mutation of one allele may exert an effect because the abnormal gene product eliminates the function of the remaining normal gene product (dominant negative effect). Alternatively, dosage effect may occur with the loss of one allele leaving insufficient normal gene product to maintain normal phenotype.[14] The complex alterations in oncogenes and suppressor genes have been shown to accumulate in the adenoma-carcinoma sequence with evidence of a preferential order.[15,16] Altered DNA methylation is an especially early event, evident even in small adenomas.[17,18] Ahnen points out the potential benefits of this increasing knowledge in identifying high-risk populations for better prevention, screening, and intervention strategies to augment or replace current cytotoxic therapy.

One of the frustrating aspects of the molecular genetics of colorectal carcinoma is the slow rate of the clinical application of knowledge to improved patient management. True, patients who have inherited the abnormal gene for the adenomatous polyposis syndrome can now be identified before the appearance of colorectal adenomas through the use of linkage analysis with molecular genetic probes near the APC gene. The same results can be obtained in most families, however, by careful indirect ophthalmoscopic examination of the retina for pigmented ocular fundic lesions manifested in affected persons at birth.[19,20] In addition, linkage analysis requires the availability of DNA from known affected family members. As a consequence, patients with a new mutation of the APC gene, as contrasted with familial cases, cannot be identified by linkage analysis. Even more frustrating, the adenomatous polyposis syndrome accounts for far less than 1% of all colorectal cancers, and the hereditary nonpolyposis form appears to account for about 5%. Thus, the successful application of molecular genetics in these syndromes will not make much of a dent in the overall morbidity and mortality from colorectal carcinoma in the US population. On the other hand, if the hypothesis of an inherited predisposition to apparently sporadic colorectal cancer is borne out and clarified, molecular genetics may lead to more accurate risk assessment for the general population.

For screening and early detection of the disorder, the field of molecular genetics also has potential application. Perhaps detection in the feces of DNA with characteristic molecular genetic abnormalities from shed tumor cells may supplant the woefully inadequate fecal occult blood testing that is the current mainstay for screening. In the areas of surgical and medical therapy, molecular genetics may supplement staging in assessing the prognosis of patients with colorectal cancer: Primary tumors with deletion of the DCC gene, deletion of the p53 gene, or high fractional allelic loss (a high proportion of evaluable nonacrocentric autosomal arms showing deletion) are associated with a poorer prognosis.[8] The application of molecular genetics may eventually help in making decisions about the type of surgical resection—local excision versus abdominoperineal resection for rectal carcinoma—and in selecting patients for adjuvant chemotherapy and radiotherapy.[1] These possible applications require additional investigation. We can even dream of gene therapy to correct key molecular genetic abnormalities if the technology becomes available: Inserting in vitro wild-type p53 gene into a colonic carcinoma cell line lacking the p53 gene product dramatically suppressed colony formation and DNA synthesis in the subpopulation of tumor cells that expressed the inserted gene.[21] Alternatively, pharmacologic agents to mimic normal gene function in tumor cells may be feasible to correct their neoplastic characteristics.

The next several years should be exciting ones for research in the genetics of large bowel cancer. Let us hope that the results will benefit the large number of patients afflicted with the disease and not lead to only knowledge for knowledge's sake.

STANLEY R. HAMILTON, MD
Department of Pathology and Oncology Center
The Johns Hopkins University School of Medicine and Hospital
Baltimore, Maryland

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Hypocholesterolemia and Malabsorption in HIV Infection

To the Editor: Hypocholesterolemia has been noted to occur in the acquired immunodeficiency syndrome (AIDS) and has been associated with the malnutrition and cachexia often seen in end-stage AIDS.[1,2] There is, however, a paucity of published data quantifying serum cholesterol levels in AIDS and almost no data on when in the course of human immunodeficiency virus (HIV) infection hypocholesterolemia occurs.

We retrospectively reviewed the charts of 68 HIV-infected patients, including 64 men and 4 women. Of these patients, 22 had more than 500 per μl T4-helper cells, 16 had 200 to 500 per μl, and 30 had less than 200 per μl T-helper cells. We compared serum cholesterol levels in these patients with published mean cholesterol levels in the American population, adjusted for age and sex.[3]

Hypocholesterolemia was common in all three patient groups. In patients with less than 200 per μl T-helper cells, 90% (27 of 30) had cholesterol levels (mean, 140 $\pm$ 71 mg per dl) in the lowest 25% of the US population with 73% (22 of 30) having cholesterol levels (mean, 134 $\pm$ 65 mg per dl) among the lowest 10% of the US population. Patients with 200 to 500 per μl T-helper cells had only slightly higher cholesterol levels, with 75% (12 of 16) having levels (mean, 143 $\pm$ 30 mg per dl) among the lowest 25%, and 56% (9 of 16) with cholesterol levels (mean, 135 $\pm$ 24 mg per dl) in the lowest 10% of the US population.

Surprisingly, patients with more than 500 per μl T-helper cells also had cholesterol levels much lower than the national means. In this group, 81% (18 of 22) were noted to have cholesterol levels (mean, 146 $\pm$ 76 mg per dl) in the lowest 25% of the US population, with 59% (mean, 131 $\pm$ 61 mg per dl) falling into the lowest 10% of the American population [3] Aspartate aminotransferase levels were measured in 12 of the 18 patients with the lowest cholesterol levels in this group of patients, with 10 of 12 patients having values within the normal range (11 to 32 U per liter) and 2 patients having mild elevations only (49 and 56 U per liter, respectively). Serum albumin levels were within the normal range in all 12 of these patients.

Our data suggest that hypocholesterolemia is a common feature of HIV infection throughout the range of disease. Hypocholesterolemia is frequently associated with malnutrition, malabsorption, or hepatic dysfunction. Hepatic dysfunction appeared to be rare in our patients with early HIV infections (T-helper cells > 500 per μl). Inadequate diet and malabsorption have been frequently noted previously in AIDS patients.[4,5] The frequency of hypocholesterolemia observed here suggests that they may occur in early HIV infection. Caution is needed in this interpretation, for our data are largely confined to adult male patients in a limited geographic area and may not reflect HIV infection in children, women, or patients in other parts of the United States or the world. Moreover, cholesterol levels are a relatively nonspecific indicator of malabsorption and malnutrition; the normal albumin values at least raise the question of whether another mechanism is responsible for the hypocholesterolemia. Nevertheless, we think that further study of the prevalence and significance of hypocholesterolemia, and possibly of malabsorption, in early asymptomatic HIV infection is warranted.

GREGG COODLEY, MD
MARCIA KERENSKY COODLEY, MD
Department of Medicine
Division of General Medicine
Oregon Health Sciences University
3181 SW Sam Jackson Park Rd, L475
Portland, OR 97201-3098

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The International Medical Corps

To the Editor: I would like to inform your readers about the service opportunities that exist with the International Medical Corps.

In early 1984, I read about the destruction of Afghanistan's health care system caused by the 1979 Soviet invasion and subsequent occupation. Most of the country's 1,500 physicians had been executed, imprisoned, or driven into exile. All humanitarian relief organizations had been ordered out of the country. Land mines were crippling and maiming thousands of civilians, and once-controlled diseases had reappeared. In May 1984, I went to Afghanistan and established the first American-supported medical surgical unit. I realized, however, that emergency assistance was not enough. If medical care were to have a lasting effect, the training of new medical personnel was essential. This led to the idea of an international medical corps that would train local health workers to care for their own people and to develop a sustainable and lasting health care system.

Founded by US physicians and nurses in 1984, the International Medical Corps (IMC) was established to provide health care through training to countries in crises whose health care systems have been destroyed. Since that time, the IMC's achievements in Afghanistan have included the building and supply of 59 clinics and hospitals in 24 provinces throughout rural Afghanistan. Over 200 medics have graduated from our medic training program based in Peshawar,

Pakistan. This past year, new training initiatives began. The IMC started an eight-month program to upgrade the clinical skills of Afghan physicians, began a four-month program to train Afghans as field microscopists, and conducted a formalized retraining program for previously trained medics. Gradually, Afghanistan's shattered health care system is being rebuilt.

In addition, the IMC has expanded its services to other regions of the world. In Honduras, health care services were provided to more than 130,000 Nicaraguans displaced by civil war. In southeast Angola, the IMC is conducting an immunization program to inoculate 60,000 children and women of childbearing age and to train local personnel. This program also includes emergency food, agricultural assistance, and nutritional and water assessments. Future health care and training projects are planned for other African countries, Central America, and for Cambodia and Kurdistan.

The IMC is the compilation of its medical personnel, many of whom volunteer to work under difficult conditions. Many challenging opportunities exist in the international health care field. I invite you to join our corps and train people to help themselves.

For further information on IMC programs, your readers can call the Recruitment Department at (213) 670-0800. Travel expenses, room, board, medical insurance, and a monthly stipend are provided.

ROBERT R. SIMON, MD
Chairman of the Board
International Medical Corps
5933 W Century Blvd, Suite 310
Los Angeles, CA 90045

Preventing the Contact Dermatitis Caused by a Transdermal Clonidine Patch

To the Editor: The centrally acting antihypertensive agent, clonidine, is now available in a transdermal treatment form and has been shown to be highly effective in the control of hypertension.[1-3]

This "Catapres-Transdermal Therapeutic System" (Boehringer Ingelheim, Ltd) is a multilayered skin patch in three sizes that continuously delivers either 0.1, 0.2, or 0.3 mg of clonidine systemically and daily for seven days before being replaced. With its use, patient compliance is greatly enhanced and the "steady state" of drug delivery decreases the incidence of adverse side effects, except for one troublesome problem—an erythematous, pruritic rash beneath the patch in about 12% to 20% of patients.[2,3] The rash may occur with treatment with all three patch sizes and is more common in white patients. It frequently causes patients to discontinue the use of transdermal therapy.

My several attempts to prevent this rash—more frequent changes of the patch or the use of steroid creams around the patch—all resulted in failure. Three years ago I began pretreating the skin application site with an aerosolized spray medication containing beclomethasone dipropionate. The results have been gratifying.

This anti-inflammatory agent is marketed as Vancenase Nasal Inhaler (Schering) and is contained within an aerosol canister with a propellant that dries instantly on contact with the skin, thereby creating ideal conditions for clonidine patch application. The original Vancenase is used, not the aqueous preparation.

In this pretreatment, the skin application site is first cleansed with an alcohol pledget and allowed to dry. The center of the site is marked and "bracketed" with four metered doses at close range of the aerosolized beclomethasone. The patch is then applied in the usual fashion to this prepared area.

In three years, I have encountered 15 patients with a "patch rash" and have treated all of them in this manner. In 12 patients, the rash has been prevented as long as they continued this pretreatment before applying a clonidine patch. When they failed to do so, the rash promptly reappeared, only to disappear when the beclomethasone spray was again used. In the 3 patients who did not respond to this pretreatment, the patches were discontinued, and oral agents were employed.

The 12 patients who did respond favorably have now been observed every 4 to 12 weeks for an average of 15 months without any reappearance of the contact dermatitis.

The good control of the hypertension in these 12 patients has not deteriorated with this treatment. No significant changes in their therapeutic regimens have been made during this follow-up period. This would indicate that the beclomethasone spray does not diminish the absorption or action of the clonidine applied to the skin surface.

Clinicians and patients alike have applauded the use of the transdermal clonidine patch. It is regrettable that contact dermatitis sometimes mars its performance. The pretreatment procedure described may allow us to continue this effective treatment in many of our hypertensive patients.

JOHN A. McCHESNEY, MD
Hypertension Clinic
University of California, San Francisco, Medical Center
Room 478-A, Box 0320
400 Parnassus Ave
San Francisco, CA 94143

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Possible Complications of Acupuncture

To the Editor: I read with great interest the report by Wright and colleagues in the January 1991 issue on bilateral tension pneumothoraces resulting from acupuncture.[1] Eight years ago I saw a similar case of bilateral tension pneumothorax in a nonasthmatic patient that was initially mistaken for an anaphylactic reaction.

Report of a Case

The patient, an elderly Chinese man, was brought to the emergency department by ambulance in severe respiratory distress. He was brought from an acupuncture office where he had just received treatment by acupuncture for unilateral shoulder pain. His skin was covered with oil of wintergreen.

On arrival, he had tachypnea, was unable to speak, and he had hypotension with a systolic blood pressure of 80 mm of mercury and sinus tachycardia. He was diaphoretic with marked use of the accessory muscles of respiration. Auscultation of the chest revealed faint inspiratory and expiratory wheezing symmetrically. The trachea was midline. The patient was promptly intubated and was administered intrave-

nous epinephrine, diphenhydramine, aminophylline, and methylprednisolone sodium succinate for presumed anaphylaxis to the liniment used in the acupuncture. A chest x-ray study was done that showed bilateral, nearly complete pneumothoraces. Bilateral chest tubes were placed, which resulted in a prompt resolution of the hypotension and respiratory distress. He was discharged well several days later and was thought to have no underlying pulmonary disease.

This case, and that reported by Dr Wright and associates, indicate a potentially lethal complication of thoracic acupuncture. I am also aware of a number of patients who have had unilateral pneumothorax related to attempted corticosteroid injection of the shoulder or thoracic trigger points. Practitioners in any field of medicine who use thoracic injection techniques must exercise caution in the depth of insertion and be aware of the potential for pneumothorax.

DAVID WILLMS, MD
Pulmonary/Critical Care Center
Sharp Memorial Hospital
7901 Frost St
San Diego, CA 92123

REFERENCE

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Carbon Monoxide Poisoning

To the Editor: We read with interest the report by Gasman and colleagues regarding an indoor barbecue and carbon monoxide poisoning in the December 1990 issue.[1] We have encountered a similar group of patients that underscores some of the authors' points:

Two 31-year-old non-English-speaking women were brought to the emergency department by paramedics, who suspected the patients had food poisoning. They had abdominal pain, nausea, vomiting, dizziness, and headache. One had had a single episode of diarrhea. They had shared a meal of barbecued beef. Three other members of the household had experienced similar but milder symptoms that did not require treatment.

The results of a physical examination of both patients were normal. On further questioning, the women admitted that the beef had been prepared on a barbecue stove in their closed apartment. They had been reluctant to provide this information to the paramedics because, having been in the United States for only a brief period of time, they assumed the paramedics—because of their uniforms—had police functions.

Once this item of history had been obtained, the patients were placed on 100% oxygen therapy. Carboxyhemoglobin levels were measured and found to be 38.3% and 31.9%. The other members of the household were called and evaluated. All had normal findings on physical examinations. Carboxyhemoglobin levels were 25.5%, 21.2%, and 18.5%.

These cases underscore the similarity that carbon monoxide poisoning may display to food poisoning, especially when more than one patient is involved. The difficulty of obtaining an accurate history because of language barriers and social background may enhance the challenge of arriving at the correct diagnosis.

GEORGE STERNBACH, MD
Emergency Medicine Service
JOSEPH VARON, MD
Department of Medicine
Stanford University Medical Center
Stanford, CA 94305

REFERENCE

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* * *

To the Editor: We read with great interest the report by Gasman and co-workers regarding carbon monoxide (CO) poisoning in a family using charcoal for indoor cooking purposes.[1] The article did an excellent job of highlighting a recurrent and insidious environmental health hazard. The authors made a few technical points, however, that merit further comment.

The authors quote a normal range for carboxyhemoglobin (COHb) saturation of less than 0.150 (<15%). Most observers agree that COHb levels as low as 10% to 15% can be responsible for headaches and dizziness. A 1989 study implicated carboxyhemoglobin levels as low as 2% in reducing exercise tolerance among patients with coronary artery disease and angina.[2] Further, in a large population-based survey, 95% of nonsmokers were found to have COHb saturations below 0.02 (<2.0%) and 95% of smokers below 0.085 (<8.5%).[3] Hence, more reasonable "normal" ranges are 0.02 or less (≤2.0%) for nonsmokers and below 0.09 (<9.0%) for smokers, with an irreducible minimum of 0.003 to 0.005 (0.3% to 0.5%) due to porphyrin catabolism.

The authors also state that dissolved CO combining with cytochromes, not impaired oxygen delivery due to COHb formation, is responsible for the toxic effects of CO. They base this assertion on a 1976 report in which anemic dogs transfused with CO-saturated blood failed to show signs of CO toxicity. In studies of experimental animals perfused with a hemoglobin substitute (a fluorinated compound without special affinity for CO), however, the animals tolerated atmospheres of 3% to 5% CO—environments that would have been rapidly fatal had the primary mechanism of CO toxicity been the interaction of dissolved CO with cytochromes.[4]

The authors make the point that "patients with severe neurologic or cardiovascular symptoms or very high COHb concentrations would benefit from hyperbaric oxygen." Although hyperbaric oxygen does substantially hasten the elimination of CO and the reduction of COHb levels in CO poisoning, there have yet to be any controlled studies showing that the ultimate outcome in patients treated with hyperbaric oxygen is better than in patients treated with normobaric oxygen.

Concern over the type of event outlined in Dr Gasman's report prompted the California Department of Health Services to issue a public warning in January 1990 cautioning against the use of gas ranges and unvented gas or kerosene heaters for indoor heating, as well as the practice of using charcoal for indoor cooking. The advisory especially targeted Asian immigrants because the traditional use of charcoal for indoor cooking purposes has been previously reported within this community. We are appreciative of Dr Gasman and colleagues for again bringing this issue to the forefront.

DENNIS SHUSTERMAN, MD, MPH
Air Toxicology and Epidemiology Section
KAI-SHEN LIU, PhD, MPH
Air and Industrial Hygiene Laboratory
California Department of Health Services
2151 Berkeley Way
Berkeley, CA 94704
KENNETH W KIZER, MD, MPH
Director
California Department of Health Services
714/744 P St
Sacramento, CA 94234-7320

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* * *

Drs Gasman and Varon Respond

To the Editor: We thank Drs Shusterman, Liu, and Kizer for their useful comments. We agree that recent data suggest that COHb levels as low as 0.10 (10%) can be symptomatic and may account for a considerable number of ambulatory presentations. Regarding the mechanism by which carbon monoxide exerts its toxic effects, certainly the primary role is through impaired oxygen delivery due to the higher affinity of carbon monoxide for hemoglobin. We agree that no data suggest that the ultimate outcome would be improved through the use of hyperbaric oxygen; after all, most patients recover completely. Seriously ill patients would recover more rapidly if hyperbaric oxygen were available and employed, however.

JOHN D. GASMAN, MD
JOSEPH VARON, MD
Department of Medicine S-102D
Stanford University Medical Center
300 Pasteur Dr
Stanford, CA 94305

Reserpine as Monotherapy for Mild Hypertension?

To the Editor: Dr Pérez-Stable has done an excellent job of reviewing the management of mild hypertension in his article in the January 1991 issue.[1] There was no mention, however, of reserpine, which remains a very useful and cost-effective antihypertensive, albeit one no longer in style. It has been well established that reserpine is highly effective for mild to moderate hypertension and that its side effects compare favorably with other antihypertensives.[2] The oft-repeated warning that reserpine be avoided because of the excessive danger of depression has been put to rest by several studies.[2,3] In fact, reserpine has even less adverse effects and remains effective when used in doses of 0.125 mg daily as shown in the VA Cooperative Study.[4]

Although Dr Pérez-Stable states that "the cost of daily drug therapy need not be a predominant determinant of choosing a regimen," this may not be convincing to the patient who has a choice between reserpine, which costs less than $15 per year (total annual cost of both reserpine and thiazide should be less than $50), and angiotensin-converting enzyme inhibitors and calcium entry blockers, which may cost as much as $700 per year. Dr Pérez-Stable does mention that compliance may be related in part to the cost of medication but then unfortunately omits the least expensive antihypertensive available. Of course, it is of great benefit to clinicians to have a large number of new antihypertensives available, but that should not preclude the consideration of using an older, less fashionable drug, particularly when it has been shown to be highly effective in carefully designed prospective double-blind studies.[2] If, in addition, the medication has the special advantage of being very inexpensive, requires only one pill per day, and has a very low incidence of side effects,[5,6] I should think it (reserpine) deserves to be mentioned, even if briefly, in an otherwise excellent review article.

LAWRENCE Z. FEIGENBAUM, MD
San Francisco Institute on Aging
PO Box 7921
San Francisco, CA 94120

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* * *

Dr Pérez-Stable Responds

To the Editor: I appreciate the comments made by Dr Feigenbaum, which are worth noting. Reserpine is an inexpensive medication with limited adverse affects when used in low doses. I concur that the risk of depression has been overstated. Reserpine, however, is not included in the Joint National Committee on Detection, Evaluation and Treatment of Hypertension's list of first-line pharmacologic treatment. Used as monotherapy, reserpine is not as effective as the four types of medications that I discussed, and, therefore, I excluded it from the review. Similarly, I did not discuss other groups of antihypertensives such as α_1 blockers or central adrenergic inhibitors that may occasionally be effective as monotherapy. In practice, I have found reserpine to cause fatigue and nasal congestion, which limited its usefulness. Although in combination with a thiazide diuretic, reserpine is useful, I doubt that it will ever regain a premier position in the antihypertensive armamentarium.

ELISEO PÉREZ-STABLE, MD
Associate Professor
Department of Medicine
Division of General Internal Medicine
University of California, San Francisco, School of Medicine
San Francisco, CA 94143

Lessons From the Practice

What the Doctor Ordered

ELLIOTT B. OPPENHEIM, MD, *Bellevue, Washington*

Mrs Ritchie is a dour, precise woman whose husband is a structural engineer for the Boeing Commercial Aircraft Company. Their lives center around careful planning for the future—meticulous attention to health matters such as cholesterol levels, sufficient exercise, and a high fiber diet. Regularity in all matters is the desired result, but "This knee, Doctor, this knee knocks my schedule off . . . I cawn't wawlk," she explained in her broad north London accent. She is, in my experience with her, a woman who smiles little and who remembers surviving on potato skins and squash through the Nazi terrorism of her country.

That year, right before Christmas she got a "burst," as she calls it, of "my arthritis," where the prepatellar bursae on both knees swell up with fluid and limit her walking. "I will admit to doing a bit of gardening over the weekend . . . my daffodils needed tending and my tulip bulbs . . . they just keep me on the run." She narrated this portion of her saga without the smallest smile, missing the obvious humor. To her, gardening is important business, after all. I picture her garden looking like a horticultural operating room—that neat and orderly.

We solved the knee trouble with one of the high-powered anti-inflammatory medicines. She thanked me, and as she rose from the examination chair, cocked her head at an awkward angle, peering out over her half-glasses.

"There is something else." Rising to her full stature, wrapping her Harris tweed coat around her shoulders, neither buttoning it nor tying her scarf, she continued. "Oh, it's not important." She reconsidered and threw her emotions into reverse and I could almost feel the gears grind.

"I would like to hear what you have," I coaxed.

"I am so depressed . . . my son says I don't smile anymore," she revealed, exhaled, and then deflated, slumped into the chair. I followed her example and sat down. This was too important to put off.

"You do look down in the dumps. I wonder what it could be?"

"I don't know; I have a beautiful new home, a new car, my husband is the best anyone could ask for . . . there is nothing wrong, yet I feel so bad." She punctuated that by plucking an embroidered pink hankie from beneath her sweater sleeve at the wrist, then knotted and unknotted it as if it were a life metaphor: she was in knots.

"Maybe it is this time of year . . . so far from Wembly."

"You miss your family?"

"Oh, yes, yes . . ." she whispered. She was in pain, a pain I have known, a pain common to any person feeling the deep hollow of missing family at any time of year.

"I have a terrific idea! Why don't you go to England and see your family? You and your husband make a bunch of money, and you're both near 70. Why don't you just go?"

"Oh, Doctor." The corners of her mouth turned up slightly. "Oh, Doctor, I never do anything unless I have cautiously planned. You know how Mr Ritchie and I are."

"Mrs Ritchie, this isn't a crazy idea."

"I just don't know what we are saving for if it isn't for this," she said and knotted up her hankie once again.

"When was your last trip to England?"

"Three years ago, and it was . . . [she sucked in a breath, almost as if she were entering a dream state] . . . grand. Oh, my mother was so surprised and we saw all my friends. Mr Ritchie and I grew up together, and we lived on the same street all our lives 'til we married. Oh, just thinking about this, I feel so much better." And she smiled a broad smile, one of immense satisfaction.

"It sounds to me as if this trip would be better than any gift either one of you could ever buy at any store. These are the years when you should reap those sown crops."

"I think you are right." She smiled again with an inner ease. "If we don't go now, who knows what will happen by next Christmas?"

Mrs Ritchie folded my prescription in half, then in half again and creased it to make a perfect square. She stowed it in her purse, buttoned her coat, tied her scarf, and scurried out of my office. "I have never done anything this silly before," were her parting words to the nurse as she grinned in child-like glee.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

(Oppenheim EB: What the doctor ordered. West J Med 1991 Jun; 154:739)

Dr Oppenheim is in private practice in Bellevue, Washington.
Reprint requests to Elliott B. Oppenheim, MD, Crossroads Family Practice, 1811 156th Ave. NE, Bellevue, WA 98007.

Lessons From the Practice

Thoughts From a Third-Year Medical Student

JAMES M. KELLER, *Albuquerque, New Mexico*

MS III—Psychiatry

Sitting here overwhelmed by feelings of helplessness and hopelessness. I can only sit and watch and listen as Sandy becomes more and more disorganized and crosses the dark threshold to enter a world of schizophrenia. "Save me, save me," she calls out periodically. But the dark voice that has come to torment her has control and laughs at our concern and good intentions.

MS III—Obstetrics

The sheer terror of the moment
is almost unbearable.
Everyone in the room
must be privy to my roaring tachycardia.
The woman screams with each contraction.
Any moment I will experience crushing, substernal pain—
any moment.
Can we please turn up the heat? It's only 40 degrees C in this
labor suite.
Squatting between her legs, I have assumed the catcher's
position.
Another contraction—
Another terrifying scream—
My systole now 300—I'm going to die.
How fortunate for me that the woman's own mother keeps
shoving a video camera in my face—"to save this miracle
moment."

MS III—Pediatrics

Oh, new, beautiful babe
Allow me to hold you minutes more
To dissolve away the day
How wonderfully whole you are
Let me rock us both to sleep
And together we shall celebrate and keep
Our covenant with life.

MS III—General Surgery

"What are these?"
(Silence)
"C'mon Jimbo, identify these."
(Silence with tachycardia)
"Goddamit, you do have a teflon brain! We talked about these
last week!"
(Silence with tachycardia and profuse sweating)
"I'm going to get you a goddamn tuition refund—they
haven't taught you a goddamn thing!"

MS III—Personal

Four coffees
to mix with a path book and long night
and dim light of a diner.
Bittersweet memories from a time past—
elevator music takes me back.
Strange that change often
hinges on chance;
yet here I sit with book in hand
two thousand miles away
and the coffee tastes the same.
Four coffees
and another night away.

MS III—General Surgery

No different,
like most meals:
busy residents, busy chatter, eager-to-please students;
griping, raunchy jokes, irreverent statements,
cross-coverage shop talk:
"What a train wreck!"
"Ingenious turf!"
"My service down by one—Stevens never made it out of the
Unit."
My stomach leaps
and the echo explodes in my ears:
"Stevens never made it. . . ."
My heart races up to room 450,
and Daniel Stevens wears the same disoriented and confused
face
we've all come to imitate during his two-week stay.
Simple embolectomy,
fantastic neuromuscular recovery,
and grateful is the Stevens.
And then fluid retention
and failing mentation—
"Dr Keller, what is wrong with me?"
Assurances, encouragement, confidence.
Post-op day 12, mentation gone.
Turfed to medicine,
and then to the MICU,
and then beyond.
A confused and silly face
stares at me from an empty hospital bed
as the echo explodes in my ears:
"Stevens never made it. . . ."

(Keller JM. Thoughts from a third-year medical student. West J Med 1991 Jun; 154:740-741)

Mr Keller is now a fourth-year medical student at the University of New Mexico School of Medicine, Albuquerque.
Reprint requests to James M. Keller, PO Box 40534, Albuquerque, NM 87196.

MS III—General Medicine

This AM when I sat him up to take his blood pressure
I did not know
he would not last the day
his look of fear, though,
impressed upon me
the seriousness of his illness
did he know?
Can't get my hands clean
seems the stain of death is slow to wash
can't remember the last time I slept
a face I cannot forget
perhaps will meet me in a dream.

MS III—General Medicine

A seemingly ancient woman before me
I cannot speak her language—
nor she mine
yet she insists on telling her story
a translator will arrive soon
to save me
voice strong but sad
no teeth in sight
blank stares illuminate her blindness
she speaks deliberately, proudly
in a manner that commands respect
I try to interpret a life's story
revealed by deep, furrowed lines
of her face
such great things I could learn from her
simple cotton clothing from a different place and time
cover a gangrenous right foot
no left foot in sight
it is a second smell that concerns me—
a cancer smell
the smell of death
translator arrives—
an RN who has little time for medical students
but a lot of time for patients
I stand awkwardly, ignorant, worried
as the old woman and the young woman talk, touch, embrace
and now cry
"She has traveled 200 miles to ask you for medicine
to help her meet her death."

Critic's Choice

PSYCHIATRY: "Mr Keller, have you no soulful experience?"

OB/GYN: "Mr Keller, your behavior betrays your hatred of women."

PEDIATRICS: "Mr Keller, do you find it necessary to manhandle all of your patients like this?"

SURGERY: "Keller, you have a teflon brain—nothing sticks."

MEDICINE (sarcastically): "Thank you for that most riveting presentation on hirsutism."

RESIDENCY CHOICE: Pathology

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CARDIOLOGY. Invasive Cardiologist join noninvasive; new Cath lab; north bay area. Huge opportunity. Electrophysiologist even better. Résumé to Number 234, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602. ASAP.

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(Continued from Page 754)

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PRACTICE OPPORTUNITIES. Family Practice, Internal Medicine, and Obstetrics and Gynecology positions available in San Diego, California, Phoenix, Arizona, Seattle, Washington, and Salt Lake City, Utah. Contact Eric Bennett, PO Box 5316, Scottsdale, AZ 85261; (602) 998-4540.

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KETCHIKAN, ALASKA. University of Washington-affiliated Family Practice seeking BC Family Physician interested in teaching and providing excellent medical care. Accredited hospital in scenic southeast Alaska. 12 years of Family Medicine students and residents through WAMI program. Fee-for-service practice. Comprehensive benefits. Negotiable salary. Stable community with wide range of activities and opportunities. Contact David Johnson, MD, or Bill Henrickson, MD, Ketchikan Medical Clinic, Inc, 3612 Tongass Ave, Ketchikan, AK 99901; phone collect (907) 225-5145.

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(Continued on Page 756)

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WASHINGTON, PUGET SOUND. Full- or part-time position with expanding physician owned group. Well established, practicing adult Emergency Medicine. High level of Critical Care with excellent medical staff. Great flexibility in scheduling to enjoy the northwest. Partnership potential. Malpractice paid. ABEM certification or preparation required. Send CV to TECP, 955 Tacoma Ave S., Ste 210, Tacoma, WA 98402; (206) 627-2303.

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COASTAL CALIFORNIA. San Luis Obispo, Internal Medicine BC/BE, busy multispecialty group, eight miles to beach, excellent schools, recently rated "best small town in USA." Rewarding hospital-based practice. Guaranteed salary, malpractice covered, excellent call rotation. Call or send CV to Fran Wolke, San Luis Obispo General Hospital, PO Box 8113, San Luis Obispo, CA 93403-8113; (805) 549-4936.

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Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

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BE/BC INTERNIST sought with or without subspecialty interest to replace departing partner in busy seven member Internal Medicine practice ten miles south of San Francisco. Contact Diane Davis, MD; (415) 583-5352, 1001 Sneath Ln, San Bruno, CA 94066.

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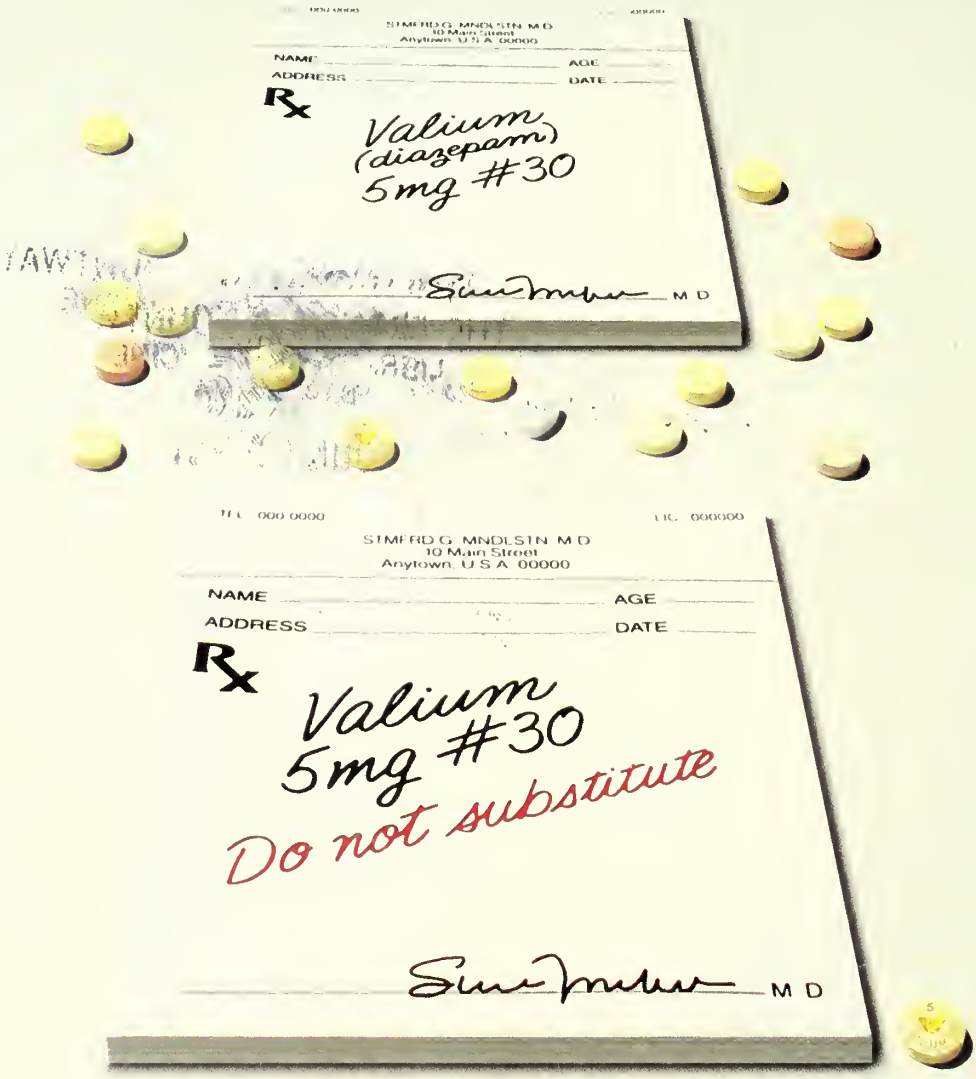

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